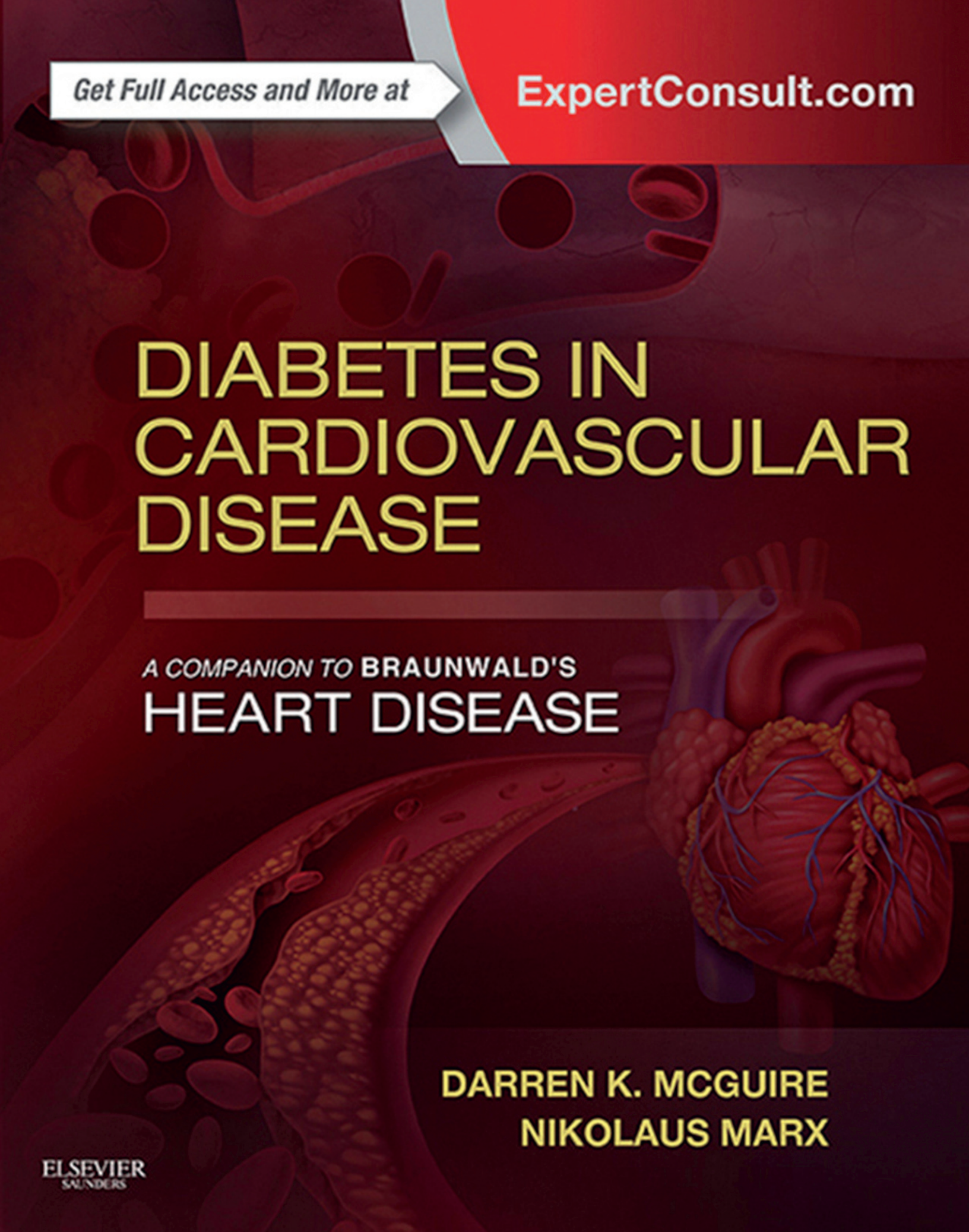
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DIABETES IN CARDIOVASCULAR DISEASE

A COMPANION TO **BRAUNWALD'S** HEART DISEASE



DARREN K. MCGUIRE
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A Companion to Braunwald's Heart Disease

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DIABETES IN CARDIOVASCULAR DISEASE

A Companion to Braunwald's Heart Disease

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To the patients around the world afflicted with diabetes, with hopes of an increasingly bright future.

Darren K. McGuire

To Nicole, and to my children, Nadine, Julian, and Florian, for their remarkable support through this endeavor.

In memory of my father Hans-Albert.

Nikolaus Marx

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Foreword

Science often takes great strides when two fields intersect and when each contributes its special knowledge, expertise, and technology to create a powerful hybrid. An example is astrophysics, in which principles of physics are applied to astronomical observations. Such intersections abound in biomedical science. For example, the relatively new field of pharmacogenetics combines the expertise of the founding sciences – pharmacology and genetics – to provide an understanding of the (sometimes enormous) differences in the response of individual patients to identical doses of drugs, and this has advanced the field of personalized medicine. In cardiology, an understanding of the electrical properties of cardiac cells and clinical arrhythmology has been combined to form the important new subspecialty of clinical electrophysiology.

The substantial increase in caloric intake and reduction in physical activity throughout the world have resulted in a pandemic of obesity that, in turn, has led to an enormous increase in the incidence of type 2 diabetes mellitus. It is widely appreciated that diabetes accelerates atherogenesis, and along with hypertension and dyslipidemia, is a cardinal risk factor for atherosclerotic disease of coronary, carotid, and other systemic arteries. Therefore, cardiologists must learn how to assess and manage diabetes in patients with this diagnosis and clinical evidence of atherosclerotic disease in the same manner in which they have become accustomed to managing hypertension and hyperlipidemia. Similarly, diabetologists (or endocrinologists) must learn how to prevent and recognize atherosclerotic complications that are responsible for the most frequent cause of death or serious illness of their patients with diabetes. As a consequence, these two specialties – cardiology and diabetology– are now "joined at the hip."

We are pleased to welcome *Diabetes in Cardiovascular Disease* as a new companion to *Braunwald's Heart Disease*. It has succeeded in placing into a single text much of what is known about the effects of diabetes on cardiovascular disease. The book is eminently readable, thorough but not encyclopedic. Part I presents the epidemiology, pathophysiology, and management of diabetes and of the metabolic syndrome. Part II focuses on the pathobiology of diabetic atherosclerosis, as well as the risk and epidemiology of this condition. The management of chronic coronary heart disease in diabetic patients is complex and is described in Part III. It involves lifestyle interventions and management of glucose, blood pressure, lipids, and anti-platelet drugs, as well as coronary revascularization. Part IV presents similar considerations for acute coronary syndromes, while Part V focuses on the special features of heart failure in patients with diabetes. Last – but certainly not least important – Part VI deals with diabetes-accelerated atherosclerosis in other vascular beds, including the peripheral and the cerebrovascular arteries, as well as autonomic neuropathy.

The 60 authors, ably led by the talented editors, Drs. McGuire and Marx, are international authorities who have provided excellent and up-to-date information in this rapidly expanding field, which is positioned at the intersection of these two specialties. The optimum care of patients with diabetes now requires a team approach involving both diabetologists and cardiologists (as well as nephrologists, neurologists, and ophthalmologists). It is likely that, if the incidence of diabetic cardiovascular disease continues to mushroom, it may become necessary to create a new subspecialty, *Diabetocardiology*, and this book would be an excellent text to prepare physicians for this important, emerging field.

Eugene Braunwald

Douglas L. Mann

Douglas P. Zipes

Peter Libby

Robert O. Bonow

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Preface

Over the past several decades, obesity and diabetes mellitus have become an increasing problem that constitutes a global epidemic, representing one of the most important chronic disease conditions in the world with critically important public health implications. Patients with diabetes exhibit an increased propensity to develop myriad cardiovascular diseases; its key sequelae are myocardial infarction, heart failure, stroke, and cardiovascular death. Over this same time period, the cardiology community has increasingly recognized the adverse cardiovascular prognosis of patients with diabetes, with increasing understanding of the heterogeneity of efficacy of available medical and interventional strategies by diabetes status and a notable unmet clinical need to mitigate the incremental "residual" cardiovascular risk associated with diabetes. Based on these observations and resultant evolution of regulatory requirements for diabetes drug development around the world, it is only within the past few years that the cardiovascular effects and safety of glucose-lowering therapies have begun to undergo rigorous assessment in large-scale randomized cardiovascular outcome trials focusing specifically on patients with diabetes. Thus the field of cardiovascular disease in diabetes has gained momentum over the past years, resulting in joint activities and guidelines from cardiology and diabetes associations around the world, requiring and fostering a truly interdisciplinary collaborative research and clinical partnership among cardiologists, endocrinologists, primary care providers, nutritionists, exercise physiologists, pharmacists, and diabetes educators—reflected in the diverse authorship of chapters in this textbook.

The first edition of *Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease* includes 31 chapters that address the spectrum of topics relevant to the nexus of diabetes and cardiovascular disease. These chapters cover the epidemiology, pathophysiologic and genetic underpinnings, clinical presentation and consequences, and diagnostic and therapeutic approaches for prevention and treatment of high-risk diabetes patients, and review systems approaches to apply such interventions. Each of the chapters is written by international leaders in their respective fields, and for us it has been a true pleasure and honor to work with such a fabulous group of experts. They are our colleagues, collaborators, and friends and represent the remarkable interdisciplinary collaborative spirit bridging our specialties and advancing the field of science and health care for the betterment of our patients.

We believe that this book will be an invaluable resource for cardiologists, diabetologists, and all other health care providers taking care of patients with diabetes and cardiovascular disease.

We thank our many friends, our colleagues, and the experts from around the world who contributed to this book. Without their expertise and contribution the text could not have been completed.

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We offer our heartfelt gratitude to those who have supported the development of this textbook. First, to Professors Braunwald and Libby, who had the confidence to allow us to edit an addition to the family of texts with the internationally revered imprimatur of *Braunwald's Heart Disease*. Second, to our colleagues and friends around the world who accepted our invitation to author chapters and delivered such excellent content that most commonly exceeded our highest expectations. Finally, to the editorial staff at Elsevier who so ably assisted and facilitated the development of this book at every step of the way: Dolores Meloni, Angela Rufino, and Cindy Thoms. To each of you, thank you.

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PART I

DIABETES MELLITUS

1 Definition and Epidemiology of Type 2 Diabetes Mellitus

Mary Beth Weber and K.M. Venkat Narayan

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Worldwide, diabetes has reached epidemic proportions. Although diabetes encompasses a range of disorders (e.g., type 1 diabetes mellitus [T1DM], type 2 diabetes mellitus [T2DM], gestational diabetes mellitus, drug- or chemical-induced diabetes [from, for example, some second-generation antipsychotic drugs[1] and some anti–human immunodeficiency virus [HIV] drugs, as well as exposure to combination antiretroviral therapy[2]]), most cases of diabetes—approximately 90% to 95%—are T2DM (hereafter referred to simply as *diabetes*). Diabetes affects multiple systems of the body and can result in serious and debilitating complications, particularly when an individual has poor glucose control. In this chapter, we provide an overview of diabetes and its complications, describe the global burden of diabetes, discuss the causal underpinnings of diabetes, and conclude with a discussion of the future of diabetes research and prevention.

TYPE 2 DIABETES—DEFINITIONS AND OUTCOMES

Glucose intolerance ranges from impaired glucose tolerance (IGT) and impaired fasting glucose (together termed *prediabetes*, a precursor to and risk factor for diabetes) to diabetes. The diagnostic criteria for prediabetes and diabetes are shown in **Table 1-1**. Traditionally, diabetes is diagnosed by fasting plasma glucose (FPG) measurements and/or a 2-hour, 75-g oral glucose tolerance test (considered the gold standard for diagnosis of diabetes). In 2009, an international expert committee (including the American Diabetes Association [ADA], the International Diabetes Federation [IDF], and the European Association for the Study of Diabetes) recommended the use of glycosylated hemoglobin A1c (HbA1c) for diabetes diagnosis.[3]

Diabetes can result in severe morbidity and increased mortality as a result of secondary complications, which affect multiple body systems, including the cardiovascular system (cerebrovascular disease and coronary heart disease), renal system (nephropathy), eyes (retinopathy), peripheral nervous system (neuropathy), and limbs (foot ulcers, peripheral vascular disease, amputations).[6–8] For a more thorough discussion of these diabetes complications, see Chapters 7, 19, 23, 27, and 28.[6–8] Diabetes is also associated with other hitherto underappreciated complications, namely, infections, liver and digestive diseases, falls and mental illness, lung diseases, some cancers, and cognitive decline.[9] Individuals with diabetes also are at an increased risk for other conditions including erectile dysfunction, tuberculosis, sleep apnea, and periodontal disease,[6,10–12] and this population reports a lower quality of life than other groups.[13] Furthermore, individuals with diabetes have an increased risk of death from conditions ranging from cardiovascular diseases and kidney failure to infections, mental disorders, and liver disease.[9] Because of the severity of the conditions associated with diabetes, diabetes is associated with an attenuated lifespan.[14]

Diabetes-related complications are not infrequent, and they affect public health systems worldwide (**Fig. 1-1**). Diabetic retinopathy is the leading cause of blindness in adults in developed countries.[6,7] An audit of the United Kingdom's National Health System's data showed additional risk for complications caused by diabetes: compared with the general population, people with diabetes were 64.9% more likely to be admitted to a hospital with heart failure, 48.0% more likely to have a myocardial infarction (MI), 331% more likely to have an amputation below the ankle, 210% more likely to have an above-ankle amputation, 24.9% more likely to have a stroke, and 139% more likely to require renal replacement therapy.[15] In the United States, diabetes is the leading cause of nontraumatic amputations of the lower limbs, blindness, and kidney failure.[16]

Diabetes is an economically costly disease. Diabetes and its complications lead to increases in work-place

TABLE 1-1 American Diabetes Association Diagnostic Criteria for Diabetes and Prediabetes

		DIAGNOSTIC TEST		
		Fasting Plasma Glucose	OGTT*	HbA1c
Type 2 diabetes		≥126 mg/dL (7.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)	≥6.5%
Prediabetes	Impaired fasting glucose†	100-125 mg/dL (5.6-6.9 mmol/L)		5.7-6.4%
	Impaired glucose tolerance		140-199 mg/dL (7.8-11.0 mmol/L)	

OGTT = Oral glucose tolerance test.
*Two-hour, 75-g oral glucose tolerance test.
†The World Health Organization (WHO) defines impaired fasting glucose with a narrower range: 110-125 mg/dL (6.1-6.9 mmol/L).[5]
Data from American Diabetes Association: Standards of medical care in diabetes—2014, *Diabetes Care* 37(Suppl 1):S14-S80, 2014.[4]

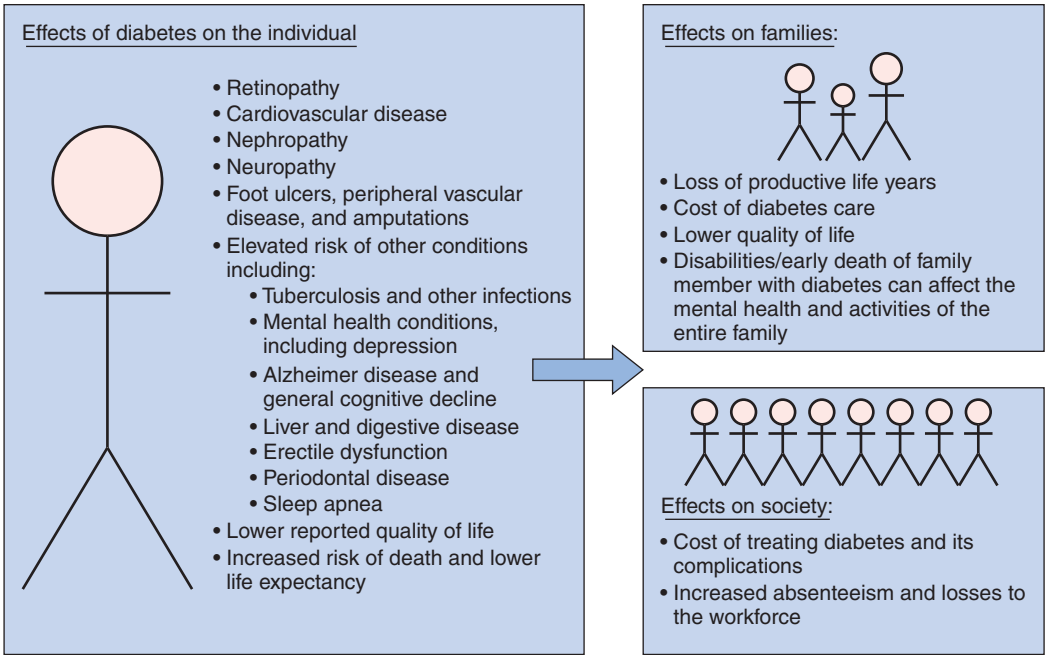


FIGURE 1-1 Secondary complications of diabetes. The effects of diabetes go beyond those on the individual—secondary complications in multiple systems of the body and increased risk of serious diseases and earlier death. Families and society as a whole are negatively affected by diabetes and its complications.

absenteeism and loss of productive life-years.[14,17] In the United States the cost of diabetes was estimated to be $245 billion dollars in 2012. This includes $176 billon dollars in direct medical costs (medications, office visits, hospitalizations, emergency care) and $69 billion in indirect medical costs (unemployment, absenteeism, and reduced productivity resulting from diabetes, and the loss to the workforce because of premature mortality associated with diabetes).[18] The costs to individuals with diabetes is also great; U.S. men and women with diagnosed diabetes have medical expenditures that are 2.3 times higher than they would have if the individual did not have diabetes.[18] In low- and middle-income countries (LMICs), the economic ramifications of diabetes can be even worse than in high-income countries such as the United States. A study conducted in India reported that few patients had health insurance, instead relying on personal savings, loans, mortgages, and property sales to pay for medical bills associated with diabetes care[19]; in this situation, the high costs of routine diabetes care and treatment of diabetes-related complications are enough to put even comfortable, middle-class Indian families into poverty.

Given the strong evidence that treatment of multiple risk factors simultaneously in patients with diabetes improves outcomes,[20,21] expert groups recommend that patients with diabetes undergo regular preventative examinations (e.g., foot and eye examinations, measures of urine protein) and manage risk factors associated with diabetes-related complications (e.g., manage blood pressure [BP], plasma lipids, and blood glucose; eliminate tobacco use; undergo treatment of albuminuria with angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB] medications; do regular exercise; be referred to a dietician).[18,22,23] Unfortunately, achievement of diabetes care targets is suboptimal. In the United States, even though there have been improvements in process of care and intermediate outcomes, two fifths of patients with diabetes have poor control of low-density lipoprotein (LDL) cholesterol, one fifth have poor glycemic control, and one third have poor BP control.[22] Data collected during a 5-year observational study in Asia, Eastern Europe, Latin America, the Middle East, and Africa show that the situation is worse in LMICs; among 9901 patients with diabetes, 36% had never had an HbA1c measurement, 11% to 36% had not been screened for secondary complications in the previous 2 years, and only 3.6% had achieved optimal LDL, BP, and HbA1c targets.[24]

GLOBAL BURDEN OF DIABETES

The burden of noncommunicable diseases (NCDs), such as diabetes, is growing worldwide, and these diseases and conditions already contribute to most mortality and morbidity worldwide. Globally, we are witnessing a major shift from communicable and undernutrition-related diseases to NCDs in adulthood.[25–27] Disability-adjusted life years (DALYs) from NCDs increased 25% between 1990 and 2010, whereas those resulting from communicable diseases and maternal, neonatal, and nutrition-deficiency disorders decreased by 26.5% in the same time period. A large proportion of the increase in the burdens of NCDs is driven by population growth and ageing, yet almost half of the increase in DALYs from NCDs between 1990 and 2010 resulted from factors other than population growth and ageing.[26]

Among NCDs, the growth of diabetes appears to be especially dramatic and worrisome. As a cause of death, diabetes has advanced in ranking from 15 in 1990 to 9 in 2010.[25] High blood glucose and associated cardiometabolic risk factors (e.g., physical inactivity, overweight and obesity, low fruit and vegetable intake) are now consistently among the top 10 risk factors for mortality globally, and across high-, middle-, and low-income countries alike.[28,29] Furthermore, high blood glucose, high body mass index (BMI), diets low in fruits and vegetables, diets low in whole grains, and physical inactivity and low physical activity were among the leading risk factors for DALYs globally in 2010, and they ranked high as risk factors for DALYs in all regions of the world.[26] Overall, over the past two decades, there has been a steady and disturbing increase in mean BMI and mean FPG globally, and this trend is affecting almost all countries of the world, barring a few exceptions, with the rate of increase most acute among developing countries undergoing industrial transformation in their economies.[30,31] In contrast, mean BP and mean total cholesterol levels have decreased globally, largely driven by decreases in high-income countries, although their levels have increased in many developing countries.[32,33]

These changes in BMI and glucose levels have translated into increases in prevalence of diabetes worldwide. The number of people with diabetes is increasing in every country of the world (**Table 1-2**), although prevalence estimates are conservative given that in 50% to 80% of those with the disease it remains undetected.[34] According to the latest IDF Diabetes Atlas, at least 382 million people worldwide had diabetes in 2013, 80% of whom lived in LMICs. By 2035 the number of people with diabetes will rise to 592 million,[34] although the growth may be greater given the overall population trends of increasing weight, aging, and urbanization.[35]

Although there are differences in diabetes risk by ethnicity (e.g., Native Americans, Hispanics, Blacks, and Asians in the United States have higher risks than non-Hispanic whites; Indians in the United Kingdom have higher risks than their Caucasian counterparts; Indians have higher risks than Chinese and Malays in Singapore),[36–38] it is generally true that the rise in diabetes prevalence is affecting all ethnic groups.[34] Similarly, both genders are affected by the increasing prevalence of diabetes.[34] As a consequence, on a global level the number of people with diabetes is projected to increase between 2013 and 2035 in every continent (+109% increase in Africa; +96% in the Middle East and North Africa; +71% in South-East Asia; +60% in South and Central America; +46% in the Western Pacific; +37% in North America and the Caribbean; and +22% in Europe; see **Table 1-2**).[34]

The steepest growth in the number of people with diabetes is occurring in LMICs. In fact, 7 of the top 10 countries worldwide in terms of number of people with diabetes are already LMICs, and by 2030 only 1 of the top 10 countries will be other than an LMIC (**Table 1-3**).[34] The number of adults with diabetes in LMICs is expected to increase at a pace that far exceeds that of developing countries (69% increase in developing countries compared with a 20% increase in developed countries by 2030).[39] In terms of diabetes prevalence, the top 10 countries or territories of the world are the Tokelau (37.5%), Federated States of Micronesia (35%), Marshall Islands (34.9%), Kiribati (28.8%), Cook Island (25.7%), Vanuatu (24%), Saudi Arabia (24%), Nauru (23.3%), Kuwait (23.1%), and Qatar (22.9%).[34]

Although the burden of diabetes is already staggering, two additional patterns are a cause for further concern. First, the number of young people with diabetes is high and increasing. The highest numbers of people with diabetes worldwide are in the economically productive age group of 40 to 59 years, and half the people who die from diabetes are under the age of 60 years—a pattern of major concern to global economic productivity and development, the health and economic costs of the disease itself notwithstanding.[34,40] In 2011 there were an estimated 490,100 children aged 0 to 14 years with T1DM worldwide, and an estimated

TABLE 1-2 Numbers of People with Diabetes (in Millions), 2013 and 2035, Globally[1]

REGION	2013	2035	INCREASE
Africa	19.8	41.4	109%
Middle East and North Africa	34.6	67.9	96%
South-East Asia	72.1	123	71%
South and Central America	24.1	38.5	60%
Western Pacific	138.2	201.8	46%
North America and Caribbean	36.7	50.4	37%
Europe	56.3	68.9	22%
World	381.8	591.9	55%

Data from International Diabetes Foundation (IDF): IDF Diabetes Atlas, Sixth Edition. Brussels, Belgium: International Diabetes Federation; 2013.

TABLE 1-3 Countries with the Highest Number of People with Diabetes (20-79 years), 2013 and 2035[1]

COUNTRY	2013 (MILLIONS)	COUNTRY	2035 (MILLIONS)
China	98.4	China	142.7
India	65.1	India	109.0
United States	24.4	United States	29.7
Brazil	11.9	Brazil	19.2
Russian Federation	10.9	Mexico	15.7
Mexico	8.7	Indonesia	14.1
Indonesia	8.5	Egypt	13.1
Germany	7.6	Pakistan	12.48
Egypt	7.5	Turkey	11.8
Japan	7.2	Russian Federation	11.2

Data from International Diabetes Foundation (IDF): IDF Diabetes Atlas, Sixth Edition. Brussels, Belgium: International Diabetes Federation; 2013.

778,000 new cases of T1DM were being diagnosed each year, representing a 3.0% increase in annual incidence. Furthermore, there has been an increase in occurrence of T2DM, traditionally believed to be a disease of adults, at younger ages.[41] There is uncertainty about the actual prevalence and incidence of youth-onset diabetes, because data are limited; however, reports suggest that T2DM may account for 10% to 30% of all youth-onset diabetes patients and that certain ethnic groups (e.g., Native Americans, Asian Indians) may be at especially high risk.[42] The best-characterized data available are from the SEARCH for Diabetes in Youth study, a multicenter investigation in the United States. The SEARCH study has reported a physician-diagnosed T2DM prevalence of 0.01/1000 among 0 to 9 year olds, and among 10 to 19 year olds the prevalence ranged from 1.74/1000 in American Indians to 0.19/1000 in non-Hispanic whites.[43]

Second, whereas the growth of diabetes was largely believed to have been an urban phenomenon, a recent systematic review of diabetes in rural parts of LMICs indicates that the diabetes epidemic is rapidly spreading through rural areas across the world. The pooled prevalence of rural diabetes among LMICs was estimated to be 5.6%, and moreover, it had quintupled in a 25-year time period.[44] Although the IDF projects a 47% rise in the number of people with diabetes globally by 2030,[34] these rural data suggest that the rise may be even higher because an estimated 55% of LMIC populations worldwide live in rural areas.[44]

CAUSAL UNDERPINNINGS OF DIABETES

Diabetes results from poor insulin resistance paired with insufficient insulin secretion (**Fig. 1-2**). Under normal metabolic conditions, pancreatic beta cells can compensate for decreases in insulin sensitivity (because of, for example, increasing age, weight gain, or physical inactivity) by producing more insulin,[45] thereby maintaining glucose homeostasis and avoiding the progression from normal glucose tolerance to prediabetes and diabetes. However, when the beta cells are impaired (because of, for example, genetic predisposition or overuse[46,47]), they are unable to adjust production of insulin to respond to increased glucose levels or decreased insulin action, leading to a hyperglycemic state. Over time, frequent or consistent hyperglycemic states will result in loss in the number of beta cells (in individuals with prediabetes, beta cell mass is about 60% of normal; it is about 40% of normal in individuals with T2DM[48]) and their functional capacity,[45,48–50] making it more and more difficult for the body to maintain glucose homeostasis unassisted.

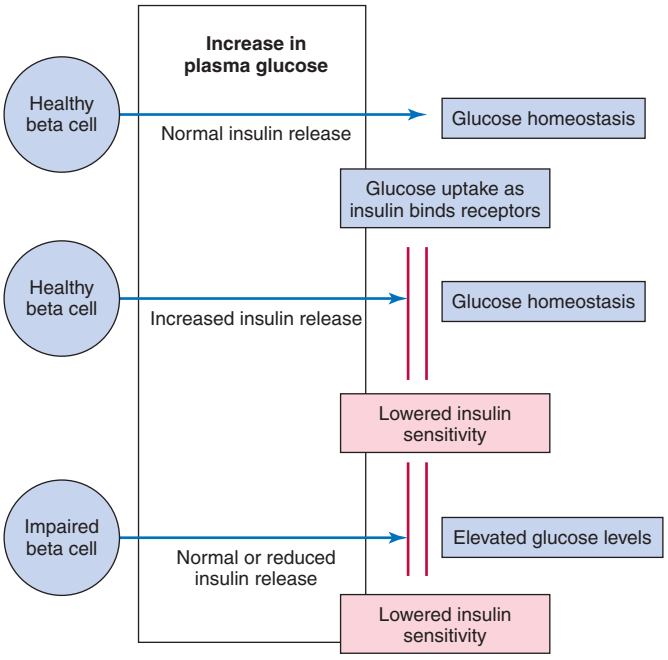


FIGURE 1-2 Beta cell response in a healthy individual compared with an individual with impaired beta cells. In a healthy individual, the beta cells are able to compensate for decreases in insulin sensitivity (because of, for example, physical inactivity or weight gain) by increasing insulin production and release, thereby maintaining glucose homeostasis in the blood. In an individual with beta cell dysfunction, however, beta cells are not able to increase insulin production sufficiently to overcome insulin resistance, resulting in sustained hyperglycemia. In the long term, this sustained elevation in blood glucose can lead to the development of prediabetes and diabetes.

Genes, Epigenetics, and Gene-Environment Interactions

The development of diabetes and its precursors, insulin resistance and beta cell dysfunction, is caused by a confluence of factors, both genetic and environmental. (For more information on the causal factors of insulin resistance, see Chapter 2.) Although insulin resistance increases with age, this is most likely the result of age-related weight gain and loss of physical activity; among nonobese, fit individuals, older people are not insulin resistant compared with younger individuals.[47] Inheritance of diabetes is polygenic, and the associated gene variants act together to confer risk[51]; however, the risk conferred by most known gene variants associated with diabetes is small[52] (the exception to this is the transcription factor 7–like 2 gene *[TCF7L2]*, a transcription factor involved in the Wnt signaling pathway[53,54]). It is likely that genes alone will not lead to diabetes in most people, although lack of underlying genetic risk may explain why many at-risk (e.g., overweight) people never develop diabetes.[55]

Family history is a strong, independent risk factor for diabetes; individuals having two parents with diabetes report a significantly higher rate of diabetes than individuals having no family history (16.7 vs. 1.8 cases of diabetes per 1000 person-years).[56] Family history as a risk factor reflects not only genetic inheritance, but also shared lifestyles and environments among families and the effects of the environment on previous generations.[57–60] Nutritional or metabolic factors can lead to temporal changes to genetic factors (so called "metabolic imprinting"), which can persist throughout life.[42,61–63] The "thrifty phenotype hypothesis" describes how maternal undernutrition (as occurs during famine or in less severe food or nutrient shortages) changes the intrauterine environment, resulting in fetal adaptations that can affect the child throughout life.[64–67] Infants born to mothers with diabetes have an increased risk of glucose intolerance, independent of genetic inheritance.[68]

The interaction of genes and environment in diabetes risk occurs throughout life and is well illustrated by considering the Pima Indians, a Native American population living in the southwest United States and Mexico. Pima Indians living in Mexico are more physically active (mean physical activity of 27.4 hr/wk) and less obese (13.2% prevalence of obesity) than Pima Indians living on a reservation in Arizona (7.6 hr/wk of physical activity and 69.3% obese). Although both populations share the same elevated genetic risk for

diabetes, the prevalence of diabetes is much higher among U.S. Pima Indians (37.5%, the highest of any race-ethnic group in the United States) than among Pima Indians residing in Mexico (8.0%).[69] A similar pattern can be seen in populations with low genetic diabetes risk. Japanese Americans tend to weigh more than their Japanese counterparts and consume a significantly greater percentage of daily calories from animal protein[70]; the prevalence of diabetes is approximately fourfold higher among second-generation Japanese-Americans than among native Japanese.[71]

Overweight and Obesity and Associated Lifestyle Behaviors

Diabetes risk is strongly associated with excess body weight[72–75]; with each one unit increase in BMI, diabetes risk increases by 12%.[76] Overweight and obesity increase diabetes risk by increasing liver and skeletal muscle insulin resistance.[77–82] How body fat is distributed, particularly abdominal adiposity, contributes to diabetes risk, independent of BMI.[77,83–85] Visceral fat, as an active endocrine organ, can lead to the development of insulin resistance and increased glucose intolerance,[86–89] through the release and accumulation of free fatty acids, cytokines, and other "toxic messengers" that impair the ability of insulin to limit glucose production in the liver and promote glucose disposal in the muscle tissue.[77–82,90]

Conversely, reducing body weight and increasing exercise counter the effects of obesity on hyperglycemia and reduce the risk for developing diabetes.[91–93] Depending on gender, baseline BMI, and age, a 10% weight loss reduces diabetes risk by 0.5% to 1.7%.[94] Exercise acts directly on glucose intolerance by enhancing insulin sensitivity[95] and improving glucose uptake,[96,97] and indirectly by decreasing concentrations of fatty acid metabolites, thereby improving insulin resistance.[78,98] Exercise also helps prevent diabetes by promoting healthy body weight. Even short-term interventions that increase moderate-intensity exercise reduce risk factors for diabetes[95,99,100] and cardiovascular disease.[101–104]

Excessive caloric intake as well as poor diet quality (e.g., low intake of dietary fiber, whole grain cereals, and low-glycemic carbohydrates or high intake of saturated and trans fats) increase the risk of cardiometabolic diseases such as diabetes.[81,105–107] On the other hand, following a healthy diet improves insulin action and reduces hepatic glucose production, thereby countering the effects of obesity on hyperglycemia.[79] A review of the data on obesity interventions concludes that low-fat diets with exercise or behavioral therapy result in prevention of diabetes and improved glycemic control.[73] Both the DASH diet (Dietary Approaches to Stop Hypertension; a low-fat, high-fiber diet rich in vegetables, fruit, and low-fat dairy products)[108] and a Mediterranean-style diet (high intake of vegetables, beans, fruits, nuts, fish, and olive oils with a low consumption of meat, high-fat dairy products, and processed foods) supplemented with extra virgin olive oil or mixed nuts[109] are associated with reduction in diabetes risk. Similarly, a healthy diet pattern (low-fat dairy, whole grains, fruits and vegetables, and moderate alcohol) significantly reduces diabetes risk (hazard ratio 0.71; 95% confidence interval [CI] 0.51-0.98) compared with several other diet patterns and reduces the 15-year risk of diabetes and death from a coronary event or nonfatal MI compared with the unhealthy diet pattern (full-fat dairy products, refined grains, processed meat, and fried foods).[110]

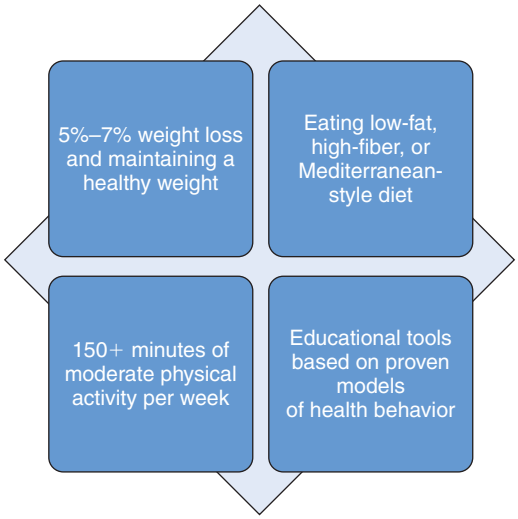


FIGURE 1-3 Behaviors associated with reduction of diabetes risk. Evidence from cohort trials and randomized studies has shown that several factors are important for successfully preventing diabetes in high-risk individuals. (1) Reaching and maintaining a healthy weight: In randomized trials a weight loss of 5% to 7% was sufficient to effect a substantial reduction in diabetes incidence. (2) Reduction in calorie intake and following a healthy diet: Both low-fat, high-fiber diets and Mediterranean-style diets have been shown to reduce diabetes risk. (3) Participation in at least 150 min/wk of moderate-level physical activity. (4) Education tools based on the science of behavior change: Diabetes prevention requires lifestyle modifications that many people find difficult to make and sustain. Health care providers should provide educational tools that are based on proven models of behavior change.

There is strong evidence from randomized controlled trials[111] that diabetes can be prevented, or at least delayed, through lifestyle education programs, programs that seek to change behaviors to improve the diets, physical activity patterns, and often body weights of participants (**Fig. 1-3**). The first randomized trial assessing lifestyle education as a tool for diabetes prevention was the Da Qing IGT and Diabetes Study.[112] In this trial, 33 health clinics in Da Qing, China were randomized to provide patients who had IGT ($N=577$) education on (1) standard diabetes prevention (control); (2) dietary improvements; (3) increasing daily exercise; or (4) improving diet and increasing physical activity. Individuals in the intervention groups all showed statistically significant improvements in diabetes risk; compared with the control arm, participants in the diet, exercise, and diet-plus-exercise groups had reductions in diabetes incidence of 31%, 46%, and 42%, respectively.[112] After 20 years of follow-up, the cumulative incidence of diabetes, after adjustment for age and clustering by clinic, was 43% lower in the intervention group (all intervention arms combined) compared with the control group.[113] The risk reduction was slightly attenuated over time, which may reflect changing behaviors of study participants or age-related weight gain or decreased activity. Alternatively, lifestyle interventions might only be able to delay diabetes (as opposed to preventing it entirely),[114] possibly because of an inability of lifestyle interventions to reverse damage to beta cell function[115] or because age-related increases in insulin resistance paired with underlying beta cell defects may counteract the improvements in insulin resistance provided by lifestyle change.

Two other trials, the Finnish Diabetes Prevention Study (DPS) and the U.S. Diabetes Prevention Program (DPP), both showed a 58% reduction in diabetes risk in participants in lifestyle programs compared with controls.[116,117] Participants in the DPS ($N=522$ overweight adults with IGT) were

provided one-on-one counseling to help them reach study goals: (1) a 5% weight loss; (2) an increase in physical activity to 30 min/day; (3) a reduction in total fat intake to less than 30% of total energy; (4) a reduction in saturated fat intake to less than 10% of total energy; and (5) an increase in dietary fiber to at least 15 g/1000 kcal. The reduction in relative risk of diabetes was lower, but still significant at 7 years follow-up (risk reduction 36%).[118] Even participants who reached only one study goal (e.g., only increased physical activity) showed improvements compared with controls; regardless of which goals were reached, the incidence of diabetes per 100 person-years was 8.4, 7.1, 5.5, 5.8, and 2.0 for participants reaching 0, 1, 2, 3, and 4 or 5 of the study goals, respectively.[118]

The DPP was the largest trial of lifestyle intervention for diabetes prevention. The study included 3234 overweight adults with IGT and elevated FPG (90 to 125 mg/dL) at 27 sites randomized to control (standard advice on lifestyle change for diabetes prevention), metformin (a glucose-lowering drug at 850 mg twice per day), or an individualized lifestyle education program (a fourth study arm testing the pharmaceutical agent troglitazone for diabetes prevention was discontinued because of potential liver toxicity of the drug). Lifestyle coaches met with lifestyle arm participants weekly for 16 sessions and monthly for eight sessions and trained participants on the behaviors and skills needed to reach the study goals of a 7% weight loss and increase in moderate-level physical activity to at least 150 min/wk. As mentioned previously, the participants in the intervention arm showed a 58% reduction in diabetes incidence compared with controls, significantly greater than the 31% risk reduction seen in the metformin arm. These results were consistent across genders and racial or ethnic groups. All age groups benefited, with oldest participants showing the greatest reduction in diabetes incidence (71% for ages 60 years or greater compared with 48% for participants aged 24 to 44 years).[116] The increased improvements among older participants were likely a result of the effects of increased exercise and weight loss overcoming age-related insulin resistance.[119] The lifestyle program was also effective in overweight and obese individuals, although those with the lowest BMIs (22 to 30 kg/m^2) had greater reductions in diabetes risk than those with BMIs of 35 kg/m^2 or greater (65% reduction in diabetes incidence compared with controls versus 51%, respectively).[116] Finally, lifestyle interventions overcame genetic susceptibility to diabetes,[116,120] with lifestyle essentially negating baseline genetic risk.

In addition to reducing risk of diabetes, lifestyle interventions have been shown to improve other markers of disease. Lifestyle participants show significant improvements in markers of inflammation, plasma lipid levels, aerobic capacity, BP, whole body insulin sensitivity, and insulin response.[79,115,121–124] Lifestyle interventions have been shown to be cost-effective for preventing diabetes.[125–127] Based on the findings of the studies described previously and other similar trials, expert organizations such as the ADA[4] and the IDF[128] recommend lifestyle changes (e.g., increased physical activity, weight loss) for diabetes prevention.

Other Risk Factors for Diabetes

Although increasing obesity and changes in diet and activity patterns can explain much of the recent increase in the number of people with diabetes, they cannot account for all of it. This has resulted in an increase in the number of researchers investigating so-called "nontraditional risk factors" for diabetes. For example, sleep, active smoking, and exposure to environmental contaminants have been hypothesized to increase risk of diabetes.

Several studies have correlated sleep debt with diabetes. In one study, the prevalences of diabetes and IGT were significantly greater in individuals sleeping either 5 or fewer or 6 hr/night.[129] Similar results were seen in an analysis of the Nurses' Health Study, a large cohort of 70,026 women: women sleeping less than 5 hr/night had a relative risk of diabetes of 1.57 (95% CI 1.28-1.92).[130] Compared with the same individuals in a fully rested situation, forced sleep deprivation of 4 hr/night for six nights was associated with lower glucose tolerance (glucose clearance after injection was 40% slower, glucose effectiveness was 30% lower, and active insulin response to glucose was 30% lower).[131] Sleep may increase diabetes risk through direct disturbances of glucose metabolism, but also through increasing obesity and obesity-associated insulin resistance (sleep deprivation is associated with upregulation of hormones associated with increased appetite, can provide more time to eat, and may decrease energy expenditure).[132] On the other end of the sleep spectrum, long sleeps (sleeping 9 or more hr/day) have also been significantly associated with diabetes and IGT.[129,130] The explanation for the association between long sleep and diabetes risk elevation is unclear.

There is strong evidence that individuals with diabetes who smoke have higher rates of both microvascular and macrovascular disease than smokers without diabetes.[133,134] Furthermore, some studies have suggested a possible relationship between smoking and insulin resistance and diabetes.[133] A meta-analysis of studies assessing this relationship reported a pooled relative risk for diabetes among smokers of 1.44 (95% CI 1.31-1.58) compared with nonsmokers. In addition, there is evidence of a dose response effect, with heavy smokers having a higher risk of diabetes than lighter smokers (relative risk 1.61 and 1.29, respectively) and former smokers (relative risk 1.23).[135] Further research is needed to determine if the association between smoking and diabetes is causal and to elucidate possible mechanisms of the association.

Recently an expert workshop was convened to summarize and evaluate evidence on the contribution of environmental chemicals to the current epidemics of diabetes and obesity. This group reported that there was sufficient evidence of an association between some environmental contaminants (e.g., arsenic in high-exposure areas, certain persistent organic pollutants, bisphenol A [BPA], some pesticides) and diabetes, but further research is needed to show causality. On the other hand, the evidence for the role of certain toxins, particularly in utero exposure to nicotine via maternal smoking, in causing obesity in humans is stronger.[136] By increasing obesity in the population, these exposures could indirectly increase diabetes incidence.

THE FUTURE OF DIABETES RESEARCH

Translating successful lifestyle intervention programs, such as the DPP and the DPS, for high-risk communities is a promising way to address the high and rising prevalence of diabetes. In public health, translational research attempts to apply proven clinical programs and public health interventions to

the broader community.[137–141] Translational research using the curricula developed for the DPS and the DPP is underway. These studies have shown promising results, with participants displaying weight loss and, in some studies, reductions in BP, FPG, plasma lipids, or diabetes risk.[142–147]

To help ensure success of the program, translational research projects should include components shared by the most effective lifestyle programs (see **Fig. 1-3**). One important component of effective diabetes prevention programs is weight loss goals for overweight participants. In the DPP, decreases in measures of adiposity (specifically, weight, BMI, and waist circumference in men and women and waist-to-hip ratio and subcutaneous and visceral fat in men) were significant predictors of diabetes risk reduction,[91] and weight loss was determined to be the most important factor in reducing diabetes risk.[148] Successful diabetes prevention programs also promote increased physical activity, most often recommending moderate physical activity for at least 150 min/wk.[91–93,112] Diabetic Prevention Study participants who increased moderate to vigorous physical activity the most had a 63% to 65% reduction in diabetes incidence compared with other study participants.[92] In addition, following a healthy, well-balanced diet that is low in fat (<30% of total calories from fat and <10% of calories from saturated fat) and high in fiber is an important component of diabetes prevention programs. The diet recommended in the DPS (a low-fat, high-fiber diet) was associated with reduced diabetes risk and had a dose-dependent effect on sustained weight loss.[149] Successful diabetes prevention programs use proven health behavior theories (e.g., the Health Beliefs model[150] or Prochaska's Stages of Change model[151]) to design behavior change curriculums. Certain skills are required to successfully implement and maintain lifestyle behavior changes. For example, individuals need to be able to identify barriers to behavior change and ways to overcome these barriers[152]; increasing social support for lifestyle changes has been shown to be an effective tool for improving outcomes in weight loss and physical activity programs[153–155]; and in the DPP, physical activity was significantly and positively associated with exercise self-efficacy.[156] Finally, in LMIC settings where the need for effective diabetes prevention programs is greatest, community-based interventions (e.g., within families and at schools, community centers, or clinics) should include culturally tailored information, promote community ownership of the program, and be designed to be cost-effective and simple to sustain and disseminate.

For the scope of the diabetes problem to be addressed, future research is needed. Although lifestyle programs are effective at reducing diabetes risk, they are unable to completely prevent the condition; after 10 or more years of follow-up, 40% to 70% of lifestyle participants still progress to diabetes, despite weight loss and/or behavior modification during the trial, indicating that lifestyle change alone may not be sufficient to prevent diabetes.[113,118,157] Also, despite a pronounced effect on peripheral insulin resistance,[79,122] lifestyle improvements may have limited effects on beta cell dysfunction.[158] Current and future research on behavior change and the psychosocial determinants of weight gain or loss, diet choices, and other lifestyle behaviors can be used to strengthen lifestyle programs. In addition, other interventions, perhaps including pharmaceutical therapies, are required to address the gaps in prevention. Better surveillance data are needed in LMIC settings, where available data indicate that most diabetes cases occur. Also, researchers are only beginning to understand the role of casual factors in different populations, and differences in how diabetes develops in different groups need to be studied (e.g., beta cell dysfunction may play a more important role than insulin resistance in the development of diabetes in Asian Indian populations[159]). Finally, there is a need to address the growing problems of poor nutrition, sedentary lifestyles, and expanding body sizes in all regions of the world, and research is required to identify effective policies, programs, and interventions to address these problems on the broader level (i.e., in cities, states, and countries).

SUMMARY

Diabetes is a serious public health problem with serious secondary complications. The global burden of diabetes is large and growing, affecting populations in every region of the world. The largest burden of diabetes occurs is in LMICs, settings with limited resources and, often, the dual public health burden of chronic and communicable diseases. Diabetes is caused by a confluence of factors, both genetic and environmental. Lifestyle behaviors, particularly physical inactivity and high-calorie, low-fiber diets, and resulting adiposity, worsen beta cell function and insulin sensitivity, resulting in a progression from normal glucose tolerance to prediabetes and diabetes in at-risk individuals. There is strong evidence from randomized controlled trials that diabetes can be prevented, or at least delayed, through lifestyle change programs; lifestyle interventions with intensive participant engagement (e.g., weekly classes) have been shown to reduce diabetes incidence by 30% to 60% in individuals with IGT or combined IGT-Impaired Fasting Glucose compared with low or no intervention. To address this epidemic, future research is needed to better understand how diabetes affects different populations and how to effectively translate, disseminate, and sustain proven diabetes prevention programs in communities around the world.

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2 Insulin Resistance

Pathophysiology, Molecular Mechanisms, Genetic Insights

Hans-Ulrich Häring and Baptist Gallwitz

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Type 2 diabetes mellitus is a chronic disturbance of glucose metabolism without the absolute insulin deficiency that is typical for type 1 diabetes. Rather, type 2 diabetes is characterized by a reduced efficacy of insulin action in different peripheral tissues (insulin resistance) as well as a disturbance in beta cell function. These two important pathophysiologic characteristics in type 2 diabetes result in an imbalance of insulin availability and insulin demand. The clinical manifestation of the disease occurs mostly in the fourth to fifth decade of life, although alarming recent data show an increase in obesity and type 2 diabetes even in adolescents.

GENETIC FACTORS

Type 2 diabetes is a polygenetic disease with heterogeneous phenotypes and different gene-environment interactions. A high genetic predisposition for type 2 diabetes has been shown in population studies (e.g., the Pima Indians) and in family studies. First-degree relatives of type 2 diabetic patients have a significantly higher risk for type 2 diabetes than persons without a hereditary or genetic risk.[1] Twin studies revealed a much higher diabetes concordance in homozygous twins compared with heterozygous twins.[2] Although the existence of these genetic factors has been known for a considerable time, it was difficult to identify specific type 2 diabetes genes until recently, when genome-wide analyses and the human genome project led to progress in this field.[3,4]

The greatest success in type 2 diabetes genetics arose from the development and use of high-density single-nucleotide polymorphism (SNP) arrays in large case-control cohorts. Most of the gene variants could be confirmed in many ethnicities, whereas others, probably because of divergent risk allele frequencies, may have higher relevance for certain ethnic groups.[4]

Recent studies also provided evidence that SNPs associated with diabetes risk act in an additive manner to increase the diabetes risk.[4–6] Although significantly contributing to the type 2 diabetes risk, these gene-gene interactions do not yet allow a substantially better disease prediction than clinical risk factors (e.g., body mass index [BMI], age, sex, family history of diabetes, fasting glucose level, blood pressure [BP], plasma triglycerides),[4,7–9] nor do they explain the heritability of type 2 diabetes.[4,5]

Beyond that, some of the diabetes-relevant genes are susceptible to persistent and partly inheritable epigenetic regulation—that is, DNA methylation and histone modifications—so gene-environment interactions are additional important factors that contribute to the complexity of type 2 diabetes genetics.[4,10–12]

Genome-wide association studies identified a series of type 2 diabetes risk loci that are for the most part associated with impaired pancreatic beta cell function.[3,13–43]

Although the underlying mechanisms by which common genetic variations within these loci affect beta cell function are not completely understood, risk variants may alter glucose-stimulated insulin secretion,[3,17,18,20,34–38] proinsulin conversion,[3,44–46] and incretin secretion or incretin action.[3] **Table 2-1** summarizes the most important diabetes genes and their functional roles.[4]

It has further become evident in recent studies that genetic variants in several diabetes risk genes may predict treatment outcome of glucose-lowering drugs. Response to thiazolidinedione therapy has been associated with peroxisome proliferator-activated receptor gamma (PPAR-γ) variations[3,47,48] in some but not all studies.[3,49,50] The genetic variants of the transcription factor 7-like 2 (TCF7L2, a transcription factor involved in the Wnt-signaling pathway and the most important genetic marker associated with type 2 diabetes) have been reported to influence disease severity and therapeutic control,[3,51] including lifestyle intervention,[3,52] and the response to sulfonylureas and possibly incretin-based therapies.[3,53]

INSULIN RESISTANCE

Type 2 diabetes, according to our present understanding, is a multifactorial disease characterized by insulin resistance of various degrees in different organs.[54] Insulin resistance is in most patients further accompanied by central obesity,

TABLE 2-1 Effects of Single-Nucleotide Polymorphisms (SNPs) in Confirmed Type 2 Diabetes Genes on Prediabetic Traits

GENE	LOCATION ON CHROMOSOME	TISSUE EXPRESSION (REPRODUCTIVE SYSTEM NOT INCLUDED)	VARIANTS (APPROXIMATE RISK ALLELE FREQUENCY IN EUROPEANS)	RISK ALLELE EFFECTS
ADAMTS9	3	Skeletal muscle, breast, thymus, kidney, prostate, pancreas, heart, lung, spinal cord, brain, all fetal tissues	rs4607103 (80%)	Unknown
CAPN10	2	Thymus, colon, bladder, brain, spleen, prostate, skeletal muscle, pancreas, heart, lymph node, lung, kidney	rs3792267 (70%), rs3842570 (40%), rs5030952 (90%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓; whole-body insulin sensitivity ↓
CDC123 \CAMK1D	10	Bone marrow, smooth muscle, kidney, prostate, colon, bladder, spleen, lung, lymph node, skin, breast, brain, liver, thymus and skin, retina, spleen, skeletal muscle, lung	rs12779790 (20%)	Insulin secretion ↓
CDKAL1	6	Bone marrow, breast, liver, spleen, prostate, retina, brain, lung, kidney, thymus, pancreas, skeletal muscle	rs7754840 (30%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
CDKN2A/ CDKN2B	9	Ubiquitous; bladder, colon, lung, spleen, skin, liver, breast, skeletal muscle, prostate, kidney, brain, pancreas, adipose tissue	rs10811661 (80%)	Glucose-stimulated insulin secretion ↓
ENPP1	6	Thyroid gland, kidney, skeletal muscle, breast, liver, skin, thymus, salivary gland, brain capillaries	rs1044498/K121Q (10%)	Whole-body insulin sensitivity ↓; insulin secretion ↓
FTO	16	Brain, pancreas, skeletal muscle, prostate, retina, heart, skin, breast, lung, kidney, liver, thymus, fetal brain, fetal kidney, fetal liver	rs8050136 (40%), rs9939609 (40%)	Overall fat mass ↑; energy intake ↑; cerebrocortical insulin sensitivity ↓
HHEX	10	Thyroid gland, brain, lymph node, spleen, liver, lung, kidney, breast, pancreas, thymus, skin, prostate, fetal pancreas	rs7923837 (60%)	Glucose-stimulated insulin secretion ↓
HNF18	17	Colon, kidney, liver, thymus, retina, pancreas, prostate, lung	rs757210 (40%)	Unknown
IGF2BP2	3	Smooth muscle, colon, lung, retina, skeletal muscle, skin, kidney, thymus, fetal liver, fetal brain, pancreas	rs4402960 (30%)	Glucose-stimulated insulin secretion ↓
JAZF1	7	Lymph node, retina, pancreas, thymus, brain, skin, liver, skeletal muscle, lung, spleen, prostate	rs864745 (50%)	Insulin secretion ↓
KCNJ11	11	Pancreas, heart, pituitary gland, skeletal muscle, brain, smooth muscle	rs5219/E23K (50%)	Insulin secretion ↓; glucose-dependent; suppression of glucagon secretion ↓
KCNQ1	11	Thyroid gland, bone marrow, prostate, heart, pancreas, lung, thymus, skin, liver, kidney	rs2237892 (90%), rs151290 (80%)	Insulin secretion ↓; incretin secretion ↓
MTNR1B	11	Retina, brain, pancreas	rs10830963 (30%), rs10830962 (40%), rs4753426 (50%)	Glucose-stimulated insulin secretion ↓
NOTCH2	1	Lung, skin, thyroid gland, skeletal muscle, smooth muscle, kidney, bladder, lymph node, breast, colon, prostate, spleen, brain, thymus, heart, liver, pancreas	rs10923931 (10%)	Unknown
PPARG	3	Adipose tissue, colon, lung, kidney, breast, spleen, skin, prostate, bone marrow, brain, skeletal muscle, liver	rs1801282/P12A (80%)	Whole-body insulin sensitivity ↓; adipose tissue insulin sensitivity ↓; insulin clearance ↓
SLC30A8	8	Pancreas, kidney, lung, breast, amygdala	rs13266634/R325W (70%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
TCF7L2	10	Brain, lung, bone marrow, thyroid gland, colon, pancreas, skin, breast, kidney, liver, thymus, prostate	rs7903146 (30%), rs12255372 (30%), rs7901695 (30%)	Incretin-stimulated insulin secretion ↓; proinsulin conversion ↓; whole-body insulin sensitivity ↓; hepatic insulin sensitivity ↓
THADA	2	Ubiquitous	rs7578597/T1187A (90%)	Unknown
TSPAN8/ LGR5	12	Spinal cord, colon, skeletal muscle, prostate, liver, lung, pancreas, kidney, skeletal muscle, skin, brain, spinal cord	rs7961581 (30%)	Insulin secretion ↓
WFS1	4	Ubiquitous	rs10010131 (60%)	Incretin-stimulated insulin secretion ↓

Data from Staiger H, Machicao F, Fritsche A, Häring HU: Pathomechanisms of type 2 diabetes genes, *Endocr Rev* 30:557, 2009.

arterial hypertension, dyslipidemia, and other risk factors for cardiovascular disease. The joint presence of these risk factors with or without manifest type 2 diabetes is summarized by the term "metabolic syndrome." The metabolic syndrome is a multifactorial metabolic disorder with a twofold to fourfold increased risk for cardiovascular disease (see **Chapter 4**).

The hormone insulin has a number of cellular effects and regulates not only glucose metabolism but also lipid and protein metabolism, as well as DNA synthesis and lipolysis (**Fig. 2-1**).[54] Any defect of these different cellular effects of insulin action can be seen as insulin resistance. In experimental medicine, the gold standard for measuring and quantifying insulin resistance is the euglycemic glucose clamp technique. This technique is too complicated and time- and personnel-consuming for everyday clinical practice; therefore a number of simpler tests for determining insulin resistance were developed. These are basically based on the assumption that a curvilinear relationship between insulin sensitivity and insulin secretion exists. In healthy patients it is possible to calculate the insulin sensitivity from the fasting plasma glucose concentration with a special formula for a hyperbolic relationship. However, this formula is not applicable for patients with a disturbance of glucose tolerance and diabetes because they show a disturbance in insulin secretion of varying degree in addition to being insulin resistant. The presently available simple tests to determine insulin resistance in patients with diabetes are based on the measurements of the fasting plasma glucose and insulin concentrations (homeostatic model assessment [HOMA])[55] or on the completion of an oral glucose tolerance test (OGTT) with measurements of plasma glucose and insulin concentrations (e.g., HOMA-IR [HOMA model for insulin resistance], insulin sensitivity index [ISI] [0,120], Matsuda index, and the Stumvoll index).[56–58] Whereas the glucose-clamp technique is a reliable method for the quantification of insulin resistance, the previously mentioned simple tests do not allow an exact quantification for a single individual. Therefore the determination of insulin resistance with these tests in an individual clinical setting is feasible only in special situations. Frequent sources of error include, for example, the incorrect performance of the OGT that will eventually lead to wrong conclusions in determining insulin resistance. In everyday clinical practice, insulin resistance can be more easily detected with symptoms such as central obesity or other factors of the metabolic syndrome. Therapeutic decisions are mainly based on these clinically visible characteristics and will lead to recommendations of lifestyle changes, body weight reduction, and pharmacologic interventions with oral glucose-lowering drugs such as metformin. It should be mentioned that insulin resistance may vary considerably depending on the patient's level of physical fitness and activity, body weight, and overall health (e.g., acute and chronic infections, tumors). Insulin resistance is a common and important risk factor for development of type 2 diabetes and cardiovascular disease.[59–63] However, insulin resistance does not always lead to diabetes even though obesity is the most important risk factor. Only patients with a disturbance in insulin secretion or other risk factors will develop diabetes.

Insulin Signaling and Cellular Mechanisms of Insulin Resistance

Insulin effects are transmitted by insulin binding to a specific transmembrane insulin receptor. The receptor belongs to the family of tyrosine kinase receptors, like the receptors for many growth factors.[64] The active receptor is a dimer of two combined subunits. Insulin effects in the intact organism are mediated almost exclusively through the insulin receptor but can also be mediated by hybrid receptors that are formed by one subunit of the insulin receptor and

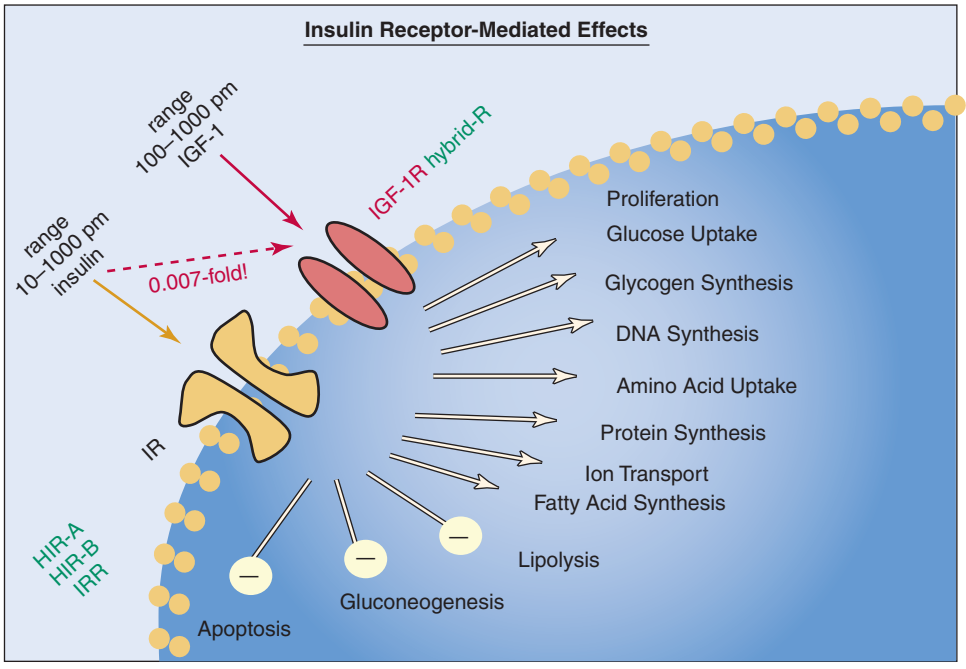


FIGURE 2-1 Insulin receptor–mediated effects. The binding of a ligand to its receptor triggers the activation of signaling pathways through effector proteins that transduce signals to several intracellular second-messenger systems, which eventually lead to biologic actions. The figure shows the insulin receptor with three different isoforms (IRR, HIR-A, and HIR-B) as well as the structurally and functionally similar receptor for insulin-like growth factor (IGF-1). The biologic actions triggered by ligand binding of insulin are depicted in a schematic manner.

another subunit of the receptor for insulin-like growth factor (IGF-1). Insulin binds with high affinity to its own receptor and with a 100 to 150 times lower affinity to the IGF-1 receptor. Therefore, insulin binding to the IGF-1 receptor does not play a notable role at physiologic insulin plasma concentrations compared with IGF-1 effects at its own receptor.[65] The affinity toward insulin–IGF-1 hybrid receptors lies between that for the insulin receptor and that for the IGF-1 receptor. The binding of insulin to its receptor leads to a cascade of cellular signals that are mostly phosphorylation and dephosphorylation events. The docking proteins IRS-1 to IRS-4 (insulin receptor substrates) have been detected as primary intracellular substrates for the postreceptor signaling. These transmit the insulin signal downstream into different cellular compartments after phosphorylation by the activated insulin receptor.[66,67] There are two distinctly different pathways in the intracellular insulin signal transmission. One pathway conveys the metabolic effects of insulin via the signaling molecules AKT/PKB; the other pathway transmits the mitogenic effects of insulin via the signaling proteins Ras/Raf/MAP kinase (**Fig. 2-2**).[54,65,67] Insulin resistance can therefore lead to a reduction of metabolic effects as well as mitogenic effects. Because redundancies and compensation mechanisms are present throughout the entire system of the intracellular signal transduction of the insulin signal, a disturbance of a single transmission element does not necessarily result in insulin resistance. Depending on the defects of the insulin signal transduction, metabolic and mitogenic effects of insulin may be affected to varying degrees.[68,69]

The Insulin Receptor, Insulin Receptor Substrates, and PKB/AKT Proteins

Numerous investigations have been carried out to investigate possible mutations in the gene for the insulin receptor in type 2 diabetes. Only very few mutations have been found that are associated with the development of insulin resistance or type 2 diabetes.[70–72] Furthermore, most studies have not shown a significant reduction in insulin receptor molecules in peripheral target tissues and organs for insulin action.[73–75] Therefore, quantitative changes in insulin receptor expression and insulin receptor mutations are not responsible for the development of insulin resistance in type 2 diabetes. It is interesting to note that a reduction in insulin receptor autophosphorylation was detected in vitro in tissues from type 2 diabetic patients in numerous former investigations.[76,77] It is hypothesized that the reduced autophosphorylation of the insulin receptor is responsible for disturbed insulin signal transduction and consequently the development of insulin resistance. The reduction in autophosphorylation and autoactivation of the insulin receptor is partially caused by modifications in the receptor molecule by an increased phosphorylation of serine residues.[78,79] The changes in insulin receptor activity are most likely secondary phenomena resulting from the metabolic changes in type 2 diabetes (e.g., hyperglycemia, dyslipidemia). Studies demonstrating normalization of the insulin receptor activity after lifestyle interventions support this hypothesis.[80–82] Only in rare patients with severe insulin resistance syndromes have insulin receptor mutations been detected that are associated with a reduced binding affinity

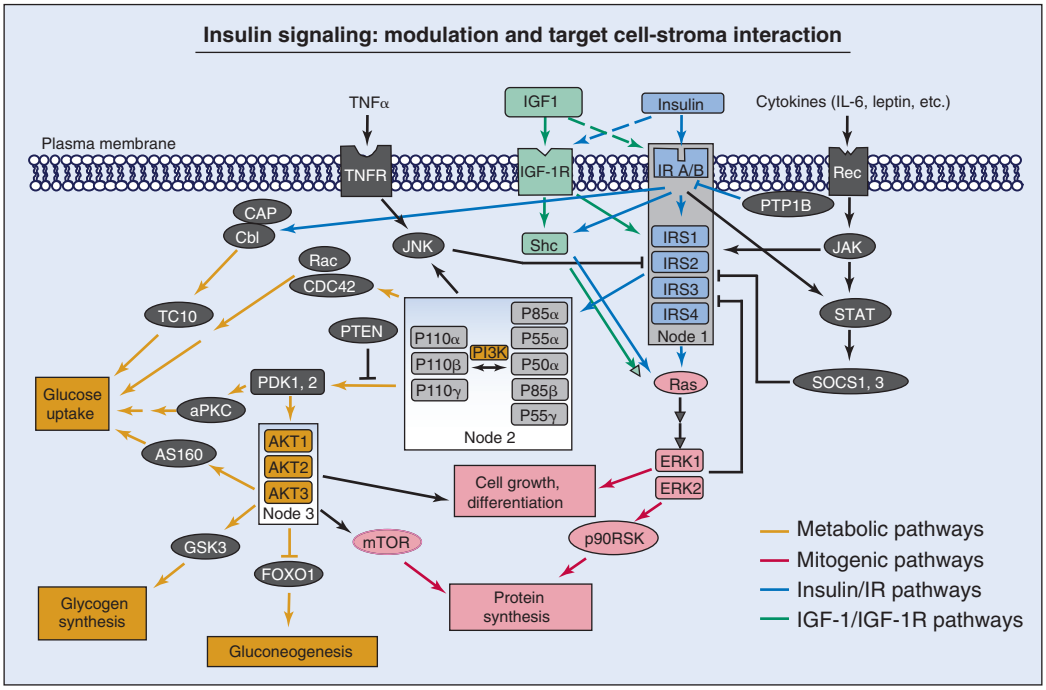


FIGURE 2-2 Insulin signaling: modulation and target cell–stroma interaction. Critical nodes form an important part of the signaling network that functions downstream of the insulin receptor (IR) and the insulin-like growth factor 1 (IGF1) receptor (IGF-1R). The important metabolic and mitogenic pathways are shown. Three important nodes in the insulin pathway are the IR and the IR substrates (IRS) 1 to 4 (node 1); the phosphatidylinositol 3-kinase (PI3K) with its several regulatory and catalytic subunits (node 2); and the three AKT/protein kinase B (PKB) isoforms (node 3). Downstream or intermediate effectors, as well as modulators, of these critical nodes include atypical protein kinase C (aPKC), AKT substrate of 160 kDa (AS160), Cas-Br-M (murine) ecotropic retroviral transforming sequence homologue (Cbl), Cbl-associated protein (CAP), cell-division cycle 42 (CDC42), extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2), forkhead box O1 (FOXO1), glycogen synthase kinase 3 (GSK3), Janus kinase (JAK), c-Jun-N-terminal kinase (JNK), mammalian target of rapamycin (mTOR), p90 ribosomal protein S6 kinase (p90RSK), phosphoinositide-dependent kinase 1 and 2 (PDK1, 2), phosphatase and tensin homologue (PTEN), protein tyrosine phosphatase-1B (PTP1B), Ras, Rac, Src-homology-2-containing protein (Shc), suppressor of cytokine signaling (SOCS), signal transducer and activator of transcription (STAT), and Ras homologue gene family, member Q (ARHQ; also called TC10). IL = Interleukin; TNF_{α} = tumor necrosis factor α; TNFR = TNF-α receptor. *(Modified from Taniguchi CM, Emanuelli B, Kahn CR: Critical nodes in signalling pathways: insights into insulin action.* Nat Rev Mol Cell Biol *7:85–95, 2006.)*

of insulin to the insulin receptor or to a diminished autophosphorylation and autoactivation of the insulin receptor. These severe insulin resistance syndromes, also referred to as *type A insulin resistance*, most often lead to glucose metabolism disorders during adolescence and are often associated with acanthosis nigricans and hyperandrogenism in women.[70,78] Other very rare insulin receptor mutations involving a complete loss of function lead to severe diseases such as leprechaunism.[83]

Functional studies on the activation of the IRSs and the phosphatidylinositol 3-kinase (PI 3-kinase) that binds to the IRS were performed predominantly in muscle cells and adipocytes of patients with type 2 diabetes. These in vitro studies revealed reduced activation of IRS-1 and IRS-2 as well as reduced PI 3-kinase/PKB (PKB = protein kinase B) activity in type 2 diabetes.[68,72,84–87] Defects in the insulin signaling cascade are therefore already present in the first steps of the signal transmission in insulin resistance and type 2 diabetes. Apart from these findings, genetic polymorphisms in the genes for the IRS proteins and the PI 3-kinase/PKB/AKT complex were found in type 2 diabetes—for example, Gly972Arg for IRS-1 and Met326Iso for PI 3-kinase.[88–91] The incidence and the functional relevance of these polymorphisms is very heterogeneous in different populations. These studies suggest that the diminished activation of IRS-1, IRS-2, and PI 3-kinase/AKT in muscle cells, hepatocytes, and adipocytes may be secondary to regulatory signal changes in metabolic disturbances. It is interesting to note that a disturbance of the metabolic signal pathway via IRS/PI 3-kinase/AKT is present in insulin resistance in type 2 diabetes, whereas the mitogenic pathway of the insulin signal via MAP kinase is not affected. In summary, in insulin resistance, a reduced cellular action of insulin is found concerning the metabolic but not the mitogenic effects of insulin.[68]

GLUCOSE TRANSPORT

The activation of the insulin signal transduction cascade leads to glucose transport into the cell. The insulin effect on the glucose transport system is mediated by a translocation of glucose transporters from the intracellular pools to the plasma membrane on the one hand, and by the activation of the transporters in the plasma membrane on the other.[64,65] There are at least 12 different glucose transporter proteins in different tissues.[92] The insulin-dependent glucose transporter GLUT-4 is the most widely expressed glucose transporter and is responsible for the largest proportion of glucose transport in muscle and adipose tissue. In addition to that, glucose-dependent glucose transporters such as GLUT-1 in the brain, GLUT-2 in the liver, and sodium-dependent transporters such as GLUT-3 in the gastrointestinal tract are also known. Investigations in muscle cells and adipocytes have been performed to elucidate whether a defect in the insulin-dependent glucose transporter GLUT-4 is responsible for the development of insulin resistance in type 2 diabetes. The results from these experiments were relatively heterogeneous and revealed a reduced expression of GLUT-4 in some studies, a defect in the translocation and activation of GLUT-4 in others, as well as an unchanged GLUT-4 expression in type 2 diabetes.[86,93–96] It is interesting to note that in studies of patients with type 2 diabetes, a reduced translocation of glucose transport vesicles to the plasma membrane was found, whereas GLUT-4 expression was unchanged.[97,98] In studies investigating possible mutations of GLUT-4 in type 2 diabetes, no functionally relevant defects were found.[99] In summary, in type 2 diabetes, a reduced capacity of insulin-dependent translocation of GLUT-4 vesicles to the plasma membrane is observed as a consequence of insulin resistance (**Fig. 2-3**).[100]

THE ROLE OF THE ADIPOCYTE AND OBESITY IN TYPE 2 DIABETES

Obesity is one of the most important predisposing factors for the development of insulin resistance and type 2 diabetes. In the past two decades, we have learned to discriminate which fat compartments contribute substantially to this development. Patients with an increased visceral (mesenteric and omental) fat mass, as well as persons with increased liver fat mass, have an increased risk for insulin resistance and type 2 diabetes.[101] This explains why measuring the waist circumference and the waist-to-hip ratio (WHR) predicts diabetes incidence more reliably than measuring the BMI. Increased subcutaneous fat depots in the hip, thigh, or gluteal region do not increase the risk for insulin resistance as long as there is no accompanying increase in visceral fat.[102] An increased subcutaneous fat accumulation around the hip and thigh is often observed in women and is termed *gynoid fat distribution,* whereas central obesity is more common in men and is termed *android fat distribution.* The causes of predominantly subcutaneous or visceral fat storage are genetic and also dependent on sex hormone concentrations and additional endocrine influences. The understanding of genetic causes for central obesity is just being unraveled, but hormones such as cortisol and androgens have already been identified as being important for the development of central obesity. Visceral fat cells express a higher number of cortisol receptors and are therefore more sensitive to react to increased plasma cortisol concentrations.[101] One hypothesis is that insulin resistance–induced obesity is caused by an overactivity of the neuroendocrine hormonal axes as well as by genetic predisposition.[101,103] One rare example of an extreme cause of central obesity and in this case a secondary cause of diabetes development is Cushing syndrome. Furthermore, hyperandrogenism in women predisposes them to central obesity.[104] These women frequently have polycystic ovary syndrome (PCOS) and an increased risk for the development of type 2 diabetes during middle age and later.

Visceral adipose tissue is now seen as an endocrine organ with respect to special functions concerning activation and secretion of numerous hormones and cytokines that mediate insulin resistance and chronic inflammation (**Fig. 2-4**).[105] Not only omental adipose tissue, but also an increased fat content in hepatocytes, muscle cells, and even intrapancreatic fat play an important role in the development of insulin resistance and even in a decrease in insulin secretion (caused by intrapancreatic fat).[4,54,63,106–109] Free fatty acids are important mediators in central obesity. Elevated free fatty acid concentrations in plasma are found in insulin resistance and in type 2 diabetes. These free fatty acids are most likely liberated by an increased lipolytic activity of the central and visceral fat depots and facilitate insulin resistance through an increased rate of fatty acid oxidation of the involved organs. Insulin and the sympathetic nervous system are important regulators of lipolysis. In central obesity, the increased sympathetic activity and a reduced

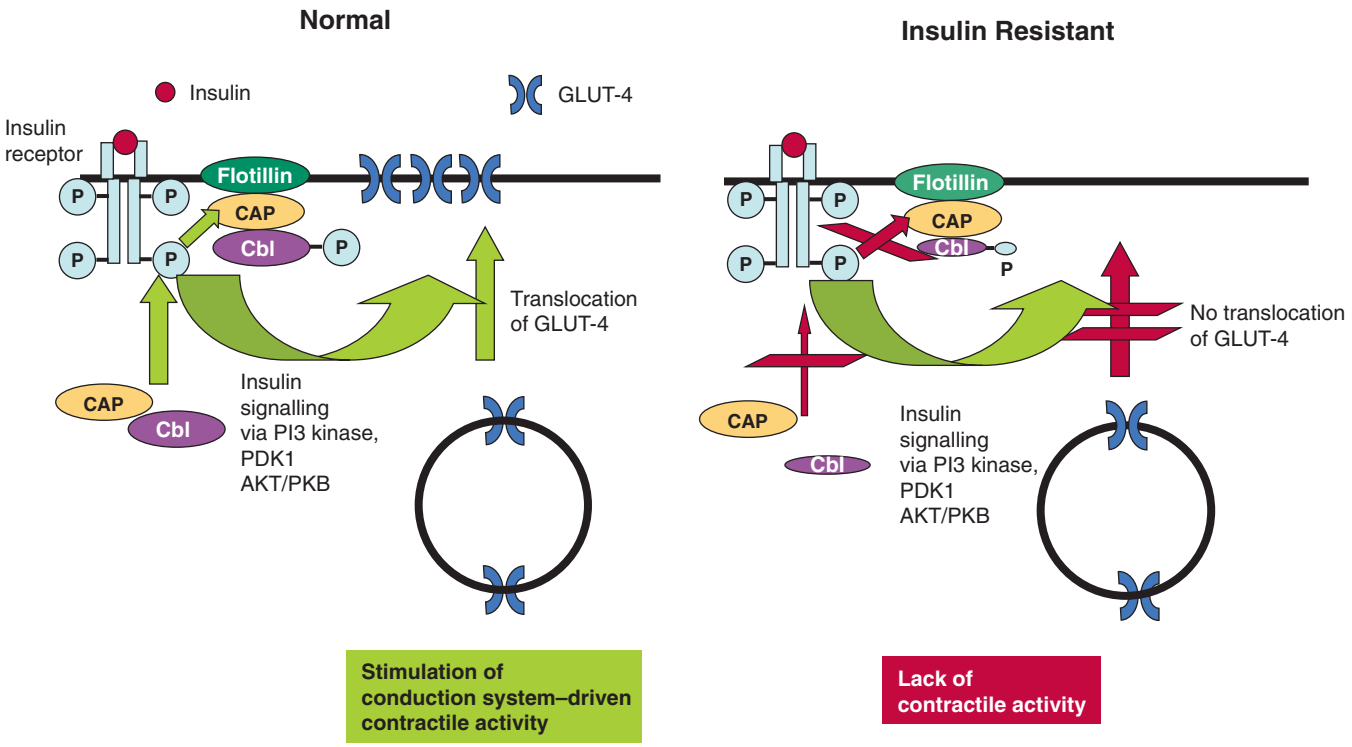


FIGURE 2-3 Differences in the regulation of GLUT-4 translocation in cardiac myocytes under normal conditions and in insulin resistance. Under normal conditions in fully differentiated cardiac myocytes (left panel), insulin stimulates the activation of the PI 3-K/PDK1/AKT signal transduction. Insulin further stimulates the phosphorylation of the proto-oncogene Cbl (Cas-Br-M [murine] ecotropic retroviral transforming sequence homologue) and its increased recruitment to a lipid raft-located complex containing flotillin and CAP (Cbl-associated protein). The joint activity of both pathways is a prerequisite for the translocation of the glucose transporter GLUT-4. In the insulin-resistant state in dedifferentiated cardiac myocytes (right panel), the stimulation of the PI 3-K/PDK1/AKT signal transduction is unchanged. Cbl, on the other hand, is reduced, and furthermore Cbl phosphorylation is impaired. As a consequence, the translocation of GLUT-4 is inhibited and the pool of available GLUT-4 is also diminished.

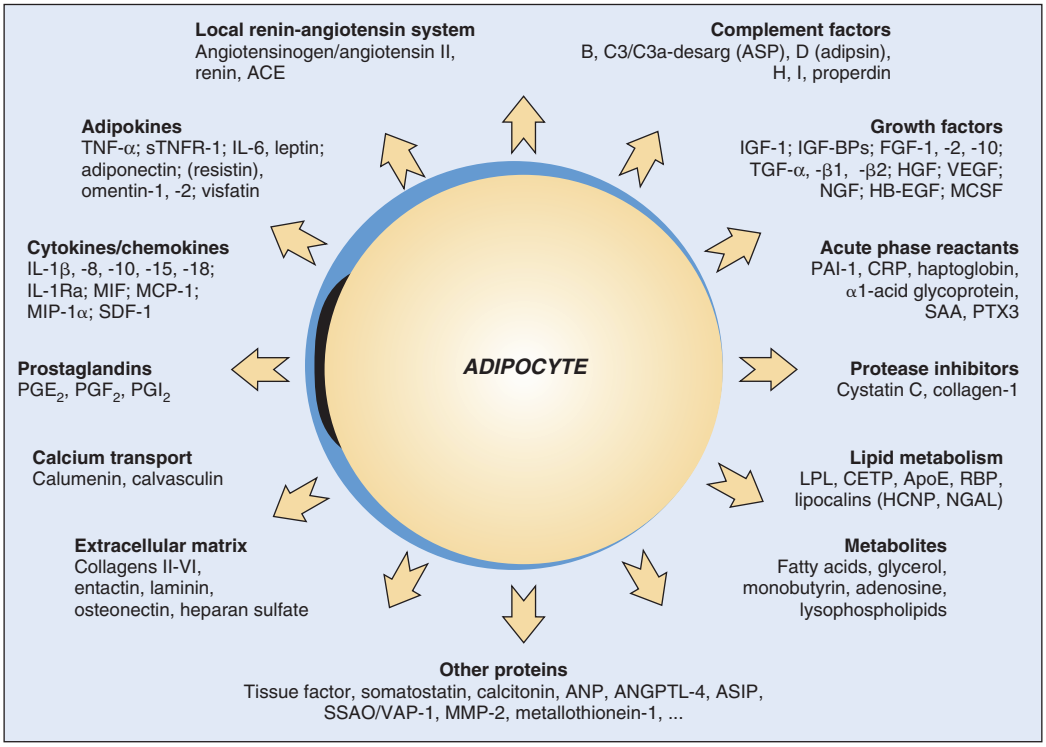


FIGURE 2-4 The adipocyte as endocrine organ. The figure shows the different hormones, cytokines, inflammatory markers, growth factors, and other transmitter molecules that are secreted by the adipocyte. These substances are involved in inflammatory processes, insulin resistance, and vascular changes. *(Modified from Staiger H, Häring HU: Adipocytokines: fat-derived humoral mediators of metabolic homeostasis,* Exp Clin Endocrinol Diabetes *113:67, 2005)*

insulin action mediate the rate of lipolysis, which results in an increase of free fatty acids.[54,62,63]

In addition to free fatty acids, numerous other factors play a role in the development of insulin resistance. In patients with insulin resistance, the insulin-sensitizing hormone adiponectin has gained much attention in the past few years, not only because circulating levels of this adipokine are markers of type 2 diabetes and an elevated risk for cardiovascular disease, but also because adiponectin is involved in the progression of these diseases.[54,110–113] Adiponectin is a protein that is synthesized and secreted by fat cells. In obese individuals, significantly reduced adiponectin plasma concentrations are observed compared with lean persons. Adiponectin is present in serum in relative high concentrations, and the serum concentrations show a negative correlation with BMI and a positive correlation with insulin resistance and even with the incidence of cardiovascular diseases.[114,115] The exogenous application of adiponectin under experimental conditions leads to an improvement in insulin sensitivity, a reduction in plasma glucose concentrations because of the activation of 5'AMP-kinase (AMP = adenosine mono-phosphate), and anti-inflammatory effects.[115–117] These effects may also be responsible for the antidiabetic and antiarteriosclerotic properties of adiponectin. Adiponectin is therefore thought to be a protective protein that is not sufficiently synthesized and secreted by adipocytes in insulin-resistant patients and patients with type 2 diabetes. Other known adipokines (e.g., leptin, resistin, retinol-binding protein, glypican-4) are currently being evaluated to determine whether they might serve as important targets for the prevention and treatment of type 2 diabetes and cardiovascular disease.[63,112,118]

Adipokines presently are the best-known "organokines", although several other classes of organokines have been identified (including myokines, lipokines, and hepatokines). Organokines are proteins exclusively or predominantly produced by and secreted from a specific tissue, but they are not simply markers of the function of their source tissue. All organokines have paracrine or endocrine actions or both (**Table 2-2**).[63,118,119]

TABLE 2-2 Important Organokines and Mediators of Insulin Resistance and Chronic Inflammation

ORGAN	IMPORTANT ORGANOKINES	REMARKS
Adipose tissue (visceral)	Adiponectin Interleukin-6 (IL-6) Leptin Omentin-1 Omentin-2 Resistin Transforming growth factor beta (TGF-β) Tumor necrosis factor alpha (TNF-α) Visfatin	For details see also Figures 2-4 and 2-5 and the text discussion of tissue- and organ-specific contribution to insulin resistance—adipose tissue (References 54, 63, 105, 132, 134)
Liver	Angiopoietin-related protein 6 Fetuin A Fetal growth factor 21 (FGF-21) Insulin-like growth factors (IGFs) Insulin-like growth factor binding proteins (IGFBP) Selenoprotein P Sex hormone binding globulin (SHBG)	For details see also Table 2-3, Figure 2-5, and the text discussion of tissue- and organ-specific contribution to insulin resistance—liver (References 63, 108, 130, 135-147)
Muscle	Brain-derived neurotrophic factor (BDNF) Erythropoietin (EPO) Interleukin-6 (IL-6) Interleukin-15 (IL-15) Interleukin-1β (IL-1β) Tumor necrosis factor alpha (TNF-α)	For details see also the text discussion of tissue- and organ-specific contribution to insulin resistance—muscle (References 89, 97, 120-127)

TISSUE- AND ORGAN-SPECIFIC CONTRIBUTION TO INSULIN RESISTANCE

Muscle

The skeletal muscle plays an important role for glucose uptake. Approximately 80% of the glucose is transported into the skeletal muscle in an insulin-dependent manner. In this respect, the skeletal muscle is an important organ involved in the development of insulin resistance. This was demonstrated in glucose-clamp experiments as well as in positron emission tomography (PET)–scan investigations that showed that in insulin resistance and type 2 diabetes, insulin-dependent glucose uptake into the skeletal muscle is significantly reduced.[97,120] Ectopic fat deposition seems also to be highly important for the development of insulin resistance of skeletal muscle. Increased intramyocellular fat depositions are found in insulin resistance and type 2 diabetes.[121–124] The ectopic fat deposition creates an altered metabolic atmosphere with increased free fatty acid concentrations and increased adipokines that lead to enhanced lipid oxidation and an increase in chronic inflammation resulting in the development of insulin resistance and diminished glucose uptake into the skeletal muscle.[122] The cause for the increased intramyocellular fat deposition in insulin resistance and type 2 diabetes is most likely a genetic disposition. The triglyceride accumulation in skeletal muscle in obesity derives from a reduced capacity for fat oxidation. An inflexibility in regulating fat oxidation, rather than a defect in fatty acid uptake, is related to insulin resistance and type 2 diabetes.[125] On the other hand, elevated circulating free fatty serum concentrations may secondarily lead to an increase in intramyocellular triglyceride accumulation.[126–128]

The humoral crosstalk between skeletal muscle and liver seems to be of interest and importance; in animal studies, an acute increase in physical activity quickly and strongly regulates the expression of a large number of genes in the liver.[63,129]

In humans, aerobic fitness specifically regulates liver fat content, but not total or visceral obesity.[63,130] Whether myokines are involved in this important crosstalk between skeletal muscle and liver in humans needs to be further investigated and characterized.[63]

In addition to insulin-dependent glucose uptake, the transport of glucose into the skeletal muscle can also be mediated by physical activity in an insulin-independent manner. This insulin- independent glucose uptake is mainly mediated by an increase in the 5'AMP-kinase concentration with the consecutive activation of the 5'AMP-activated protein kinase (AMPK). Most data indicate that this pathway, activated by physical activity, is not altered in insulin resistance and in type 2 diabetes, in contrast to perturbations of insulin-dependent glucose transport.[131]

In this respect, interleukin 6 (IL-6) produced in the working muscle during physical activity could act as an energy sensor by activating AMP-activated kinase and enhancing glucose disposal, lipolysis, and fat oxidation.[132,133] In addition to the numerous positive effects of physical activity on all aspects of the metabolic syndrome and beyond, physical fitness and training improve glucose uptake into the skeletal muscle via the AMPK pathway.

Adipose Tissue

The role of central and visceral obesity in the development of insulin resistance was described previously. On a molecular level, the mediators secreted by the adipocytes in dependence of fat mass and fat distribution play an important role in the development of insulin resistance. In addition to the free fatty acids, adiponectin and numerous inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-6, and transforming growth factor beta (TGF-β) are secreted by the adipocytes. These inflammatory cytokines cause insulin resistance via an inhibition of the intracellular insulin signaling.[54,132] In addition, they lead to inflammatory processes that are frequently observed in insulin-resistant patients. The visceral fat stores therefore mediate insulin resistance and chronic inflammation, as well as arteriosclerotic development, through their secretory capacity of adipokines and cytokines.[63,134]

Liver

One of the most important physiologic functions of the liver in glucose metabolism is to make glucose available for other organs in the fasting state, especially during the night. The regulation of hepatic glucose production is mediated by the influence of insulin on gluconeogenesis. In the postprandial state, the plasma glucose concentration rises, as do the concentrations of the incretin hormones (mainly glucagon-like peptide 1 [GLP-1]) that stimulate insulin secretion. Insulin reaches the liver directly in high concentrations via the portal vein system and physiologically suppresses hepatic glucose production, which would be counterproductive in the postprandial state, when plasma glucose is elevated already.[135] Only during the fasting state with low glucose and insulin concentrations do low insulin concentrations disinhibit hepatic gluconeogenesis, leading to sufficiently high glucose concentrations in the circulation in the fasting state. In insulin resistance and type 2 diabetes, an increased hepatic glucose production is observed that is caused by a diminished hepatocyte response to insulin failing to suppress gluconeogenesis.[136] Insulin resistance of the liver is typically detected in the clinical setting through elevated fasting glucose concentration, which is caused by the increased hepatic glucose production. Different mechanisms that lead to an increased hepatic gluconeogenesis are discussed: the insensitivity of the liver toward insulin itself on the one hand, but also elevated free fatty acid concentrations, as well as hyperglucagonemia, and increased activity of phosphoenolpyruvate-carboxykinase (PEPCK), a key enzyme of gluconeogenesis.[136–138] One important trigger for insulin resistance of the liver is the fat accumulation in this organ. Different studies have shown a correlation between triglyceride content in hepatocytes and insulin resistance within the liver.[63,108,139,140] Patients with type 2 diabetes frequently also have nonalcoholic steatohepatosis (NASH) or nonalcoholic fatty liver disease (NAFLD), which are tightly correlated with insulin resistance.[63,108] Successful implementation of a lifestyle intervention may reduce liver fat mass and may improve insulin resistance.[63,108,130] The insulin-sensitizing effect of metformin and glitazones is partially explained by the reduction of the triglyceride content in the liver.[141] NAFLD is the most common liver disease and, along with the worldwide increase in prevalence of general and abdominal obesity, NAFLD has become a prevalent general health problem in many industrialized countries. NAFLD represents a continuum of liver disease from simple steatosis to NASH and cirrhosis. Up to 20% of patients with simple steatosis will develop NASH, and in a subgroup of these patients NASH can progress further to NASH with fibrosis and cirrhosis.[63,142,143] Cirrhosis is the main risk factor for development of hepatocellular carcinoma.[63,144,145] In addition, NAFLD was identified as a strong and independent predictor of type 2 diabetes and cardiovascular disease.[63,146] Thus, much effort is currently focused worldwide on precisely quantifying liver fat content in humans for predictive and therapeutic purposes.[63,143] However, this endeavor might not be sufficient to completely understand the pathophysiology of NAFLD.

During conditions of a positive energy balance, subcutaneous and visceral adipose tissues expand in a manner that is predominantly genetically determined. Subcutaneous obesity is not strongly associated with metabolic diseases, whereas visceral obesity is a strong predictor of these diseases. Increased availability of fatty acids (resulting from increased lipolysis), increased subclinical inflammation, and dysregulation of adipokine production and release are thought to promote insulin resistance, atherosclerosis, and beta cell dysfunction. Accumulation of lipids in the liver is also largely genetically determined, and two distinct phenotypes have been identified. When hepatic detoxification processes are active, storage of lipids in the liver is not associated with metabolic diseases. By contrast, when lipotoxicity is present, hepatic glucose production increases and lipids are released, with an atherogenic profile. Dysregulated hepatokine production also contributes to the development of metabolic diseases. The important heptokines are listed in **Table 2-3**, and **Figure 2-5** shows a schematic diagram of the

TABLE 2-3 Function of Important Hepatokines In Vitro and In Vivo

Hepatokine	EFFECTS	
	In Vitro or Animal Studies	In Humans
Angiopoietin-related protein 6	Energy expenditure ↑ Obesity ↓ NAFLD ↓ Insulin resistance ↓	Insulin resistance ↑
Fetuin A	Obesity ↔/↑ Insulin resistance ↑ Subclinical inflammation ↑	Obesity ↔ NAFLD ↑ Insulin resistance ↑ Subclinical inflammation ↑ T2DM ↑ CVD ↑
FGF 21	Energy expenditure ↑ Insulin resistance ↓ Beta cell survival ↑	Obesity ↑ NAFLD ↑ Insulin resistance ↑
IGFs and IGFBPs	Insulin resistance ↔/↑/↓	Insulin resistance ↑/↓
Selenoprotein P	Insulin resistance ↑	Insulin resistance ↑ Subclinical inflammation ↑
Sex hormone-binding globulin	Sex hormone bioavailability ↑ Sex hormone signaling ↑	Obesity ↓ NAFLD ↓ Insulin resistance ↓ Subclinical inflammation ↓ T2DM ↓ Cardiovascular disease ↓

CVD = Cardiovascular disease; T2DM = type 2 diabetes mellitus.
Data from Stefan N, Häring HU: The role of hepatokines in metabolism, *Nat Rev Endocrinol* 9:144, 2013.

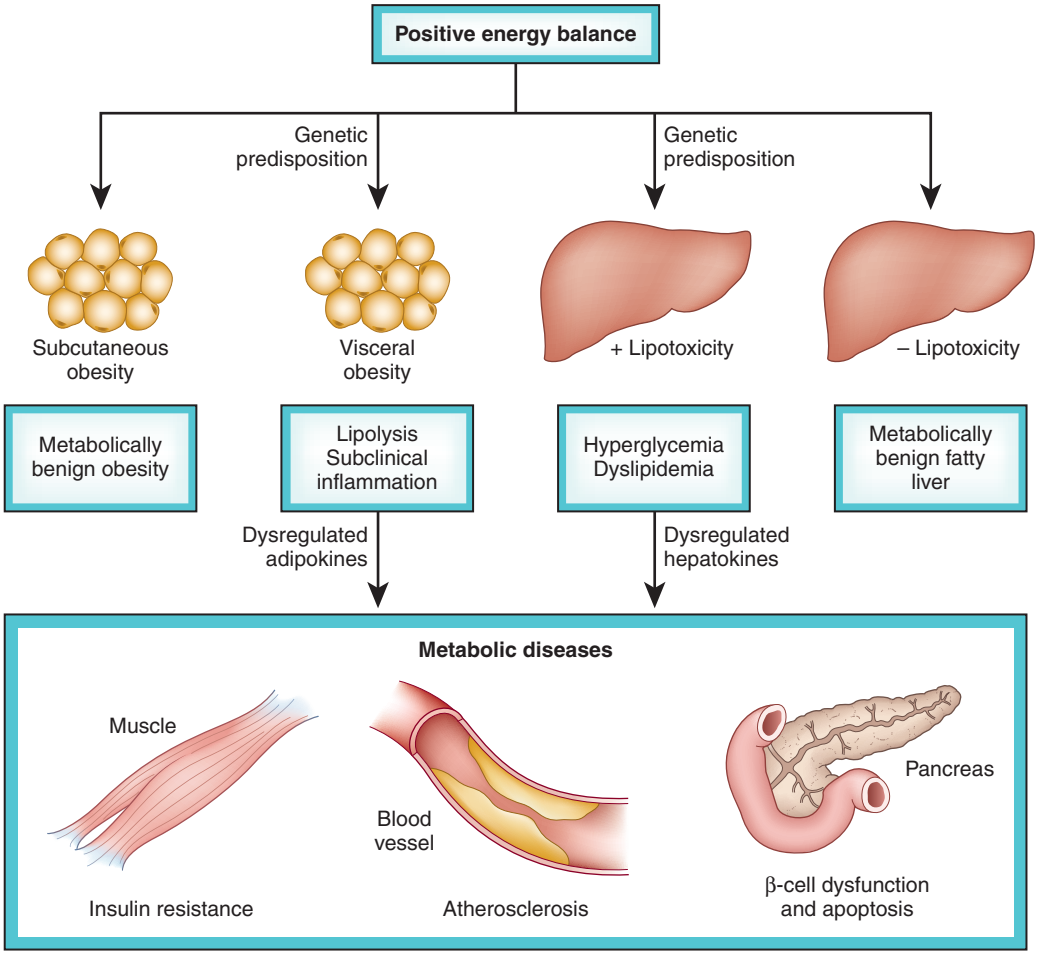


FIGURE 2-5 Novel roles of liver and adipose tissue in the development of metabolic diseases. During conditions of a positive energy balance, subcutaneous and visceral adipose tissues expand in a manner that is predominantly genetically determined. Subcutaneous obesity is not strongly associated with metabolic diseases, whereas visceral obesity is a strong predictor of these diseases. Increased availability of fatty acids (resulting from increased lipolysis), increased subclinical inflammation, and dysregulation of adipokine production and release are thought to promote insulin resistance, atherosclerosis, and beta cell dysfunction. Accumulation of lipids in the liver is also largely genetically determined, and two distinct phenotypes have been identified. When hepatic detoxification processes are active, storage of lipids in the liver is not associated with metabolic diseases. By contrast, when lipotoxicity is present, hepatic glucose production increases and lipids are released, with an atherogenic profile. Dysregulated hepatokine production also contributes to the development of metabolic diseases. *(Modified from Stefan N, Häring HU: The role of hepatokines in metabolism,* Nat Rev Endocrinol *9:144, 2013.)*

putative roles of liver and adipose tissue in the development of metabolic diseases.[63]

The glycoprotein fetuin-A is an important hepatokine. It is a natural inhibitor of the insulin-stimulated insulin receptor tyrosine kinase and induces insulin resistance in rodents. In humans, circulating fetuin-A levels are positively associated with fat accumulation in the liver, insulin resistance, the metabolic syndrome, and type 2 diabetes mellitus. In addition to inducing insulin resistance, fetuin-A is involved in subclinical inflammation and correlates positively with high-sensitive C-reactive protein (hsCRP) levels in humans. It also induces cytokine expression in human monocytes and reduces the expression of the atheroprotective adipokine adiponectin in animals. Taken together, fetuin-A may represent a pathway linking fatty liver with cardiovascular events by inducing insulin resistance and inflammation. Indeed, an investigation in the cohort of the EPIC study (European Prospective Investigation into Cancer and Nutrition; EPIC-Potsdam) revealed a link between high plasma fetuin-A levels and an increased risk of myocardial infarction (MI) and ischemic stroke. High fetuin-A plasma concentrations led to a threefold to fourfold increased risk for MI and ischemic stroke.[147]

Brain

During the past years an increasingly important role of the brain in the development of insulin resistance and obesity has been found. The brain is not only an important organ for glucose disposal, but has recently also been recognized as an insulin-sensitive organ. Insulin receptors are expressed in brain tissue.[148] A high degree of insulin sensitivity of the human brain facilitates loss of body weight and body fat during a lifestyle intervention.[149]

Furthermore, insulin has important functions in regulating satiety signals and energy expenditure within the central nervous system and therefore has an influence on the development of obesity.[150] Intracerebroventricular application of insulin promotes satiety in experimental models in animals and human studies. Neutralizing insulin effects in the brain in animal experiments leads to hyperphagia and obesity[151] and to a reduced peripheral action of insulin in the liver.[152] The results of these experiments point to insulin effects in the brain that most likely lead to a neurotransmitter response that has an influence on hepatic glucose production. The brain is therefore an important central regulator for peripheral insulin action in the liver.

BETA CELL DYSFUNCTION IN TYPE 2 DIABETES

The Role of Insulin Secretion and the Beta Cell in Type 2 Diabetes

Disturbed beta cell function and a loss of beta cell mass of the pancreatic islets play important pathogenetic roles in the development and progression of type 2 diabetes. Regarding the beta cell, a loss of insulin secretion and defects in the early phase of insulin secretion are important in the pathogenesis of type 2 diabetes. As diabetes progresses, a loss of beta cell mass is also observed. In addition, a disturbance in glucagon secretion from the pancreatic alpha cells in the islet with hyperglucagonemia also contributes to the disorder of glucose metabolism. Although insulin resistance is relatively stable in the course of type 2 diabetes, the defects in beta cell function and the loss of beta cell mass are responsible for the progressive nature of the disease.

Pulsatility

Insulin secretion is regulated through a complex interplay of glucose, hormones, incretins, amino acids, and neuronal signals, among other factors. Physiologic insulin secretion follows a pulsatile pattern; in healthy individuals, every 5 to 10 minutes insulin is secreted in a pulse.[153–155] These short-lasting insulin pulses add up to an insulin secretion profile that is repeated every 80 to 150 minutes. The pulsatile secretion of insulin is significantly more effective in lowering plasma glucose concentrations than continuous secretion.[156] Patients with type 2 diabetes already show defective pulsatile insulin secretion even before the clinical manifestation of their diabetes. This defect is characterized by a reduction in pulse frequency as well as lower amplitudes of the insulin pulses. These disturbances can be observed in glucose-dependent as well as glucose-independent fashion.[138,157,158] Insulin secreted from the beta cells reaches the liver via the portal system in the described pulsatile manner. It is degraded by approximately 60% in the liver and not distributed in the same pulsatile fashion into the systemic circulation. As a consequence of the defective pulsatile insulin secretion, hepatic glucose production is elevated.[159,160]

Glucose-Dependent Insulin Secretion

The insulin secretion response after glucose administration in healthy individuals has a typical biphasic pattern, with an immediate insulin secretion peak approximately 3 to 5 minutes after an intravenous glucose bolus and approximately 20 minutes after oral glucose administration, which lasts for around 10 minutes. This acute or first phase of insulin secretion is followed by a second phase with a slower and more sustained elevation of plasma insulin concentrations. The duration of the second phase of insulin secretion is dependent on the elevation of plasma glucose. The first phase of insulin secretion results from liberation of insulin from the fast recruitable secretory vesicles that are close to the plasma membrane of the beta cell. The second phase of insulin secretion is recruited from a less readily recruitable reserve pool of insulin vesicles. This reserve pool comprises newly synthesized insulin vesicles and so-called "storage vesicles" and is located further away from the outside cell membrane of the beta cell.[161–164] In type 2 diabetes as well as in the prediabetic state of impaired glucose tolerance (see **Table 2-4** for classification),[165] a significantly reduced or even absent first phase of insulin secretion is observed after a glucose stimulus.[166–168] This defect in the first phase of insulin secretion especially has an impact on the postprandial glucose concentrations.[169] Several mechanisms have been reported to cause the defect in the first phase of insulin secretion: chronic hyperglycemia, elevated free fatty acid plasma concentrations, and a reduction in beta cell mass.[170] Some studies indicate that the first phase of insulin secretion can be restored by normalizing glucose metabolism.[171] In addition to the described changes of the first phase of insulin secretion, the second phase is also changed in type 2 diabetes. Because of persistent hyperglycemia, the second phase of insulin secretion is often prolonged and more pronounced compared with the second phase in healthy individuals.[166] There is a reciprocal nonlinear hyperbolic relationship between insulin secretion and insulin resistance. Insulin secretion can therefore be evaluated only with respect to the amount of peripheral insulin resistance. In insulin-resistant patients with type 2 diabetes, elevated plasma insulin concentrations may be observed compared with healthy controls, but these may be inappropriately low in relation to the degree of insulin resistance or to the elevation of plasma glucose concentrations during chronic hyperglycemia and may not be sufficient to normalize the plasma glucose. The insulin secretion in type 2 diabetes is therefore insufficient and often inadequate to cover the actual demand for glucose normalization. In addition to the disturbed insulin secretion, a defect in glucagon secretion is found in type 2 diabetes. Usually, an inappropriately high glucagon secretion is observed that mediates increased hepatic glucose production.[172] This hyperglucagonemia is partially caused by the lack of the tonic inhibition of glucagon secretion by insulin and the beta cell activity.[159,160,173]

Proinsulin-to-Insulin Ratio

In addition to the described defects in insulin secretion kinetics, in type 2 diabetes a change in the proinsulin-to-insulin ratio is observed that is characterized by a higher proinsulin secretion.[174] In the secretory granules of the beta cell,

TABLE 2-4 Classification and Detection of Type 2 Diabetes and Prediabetic States with a Standardized Oral Glucose Tolerance Test (OGTT, 75 g Glucose)

TIME POINT OF GLUCOSE MEASUREMENT	NORMOGLYCEMIA	IMPAIRED FASTING GLUCOSE (IFG)	IMPAIRED GLUCOSE TOLERANCE (IGT)	TYPE 2 DIABETES
Fasting (0 minutes)	<100 mg/dL <5.6 mmol/L	100-125 mg/dL 5.6-6.9 mmol/L		≥126 mg/dL ≥7.0 mmol/L
2 hours postglucose	<140 mg/dL <7.8 mmol/L		140-199 mg/dL 7.8-11.0 mmol/L	≥200 mg/dL ≥11.1 mmol/L

Glucose measured in venous plasma.
Data from American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 36(Suppl 1):S67, 2013.

insulin and C peptide are formed by the enzymatic cleavage of proinsulin. In healthy individuals, approximately 2.5% of immunoreactive insulin originates from proinsulin or intermediate split products of proinsulin; in patients with type 2 diabetes, this proportion is much higher and amounts to approximately 8%. This finding indicates a defective or incomplete processing of proinsulin in type 2 diabetes.[175,176] It is interesting to note that in healthy individuals the proinsulin-to-insulin ratio is also dependent on the degree of peripheral insulin resistance and on the fasting plasma glucose concentration. The proinsulin proportions vary from minimally 8% under normoglycemic conditions to approximately 30% under overt hyperglycemia with glucose concentrations of 15 mmol/L.[177] It is hypothesized that chronic hyperglycemia is a continuous stimulatory impulse for insulin granules. Because of this chronic hypersecretion, matured insulin granules are depleted and immature insulin granules with a higher proportion of proinsulin prevail.[178] In addition, other mechanisms of defects in insulin biosynthesis that are not primarily dependent on hyperglycemia are discussed as being responsible for the increased proinsulin secretion in type 2 diabetes. Because proinsulin has only a very low insulin-like biologic activity, a further reduction of insulin action for insulin- sensitive organs results from the change in the proinsulin-to-insulin ratio. The increased proinsulin secretion is further seen as a marker for beta cell stress and as a predictor for diabetes development.[175,176]

Incretin Hormones and Type 2 Diabetes

The so-called "incretin effect" describes the phenomenon by which orally ingested glucose elicits a significantly more pronounced insulin response than an intravenous glucose infusion with identical changes of plasma glucose concentrations. The incretin effect is mediated by the gastrointestinal hormones glucose-dependent insulinotropic peptide (GIP) and GLP-1, which are physiologically secreted after a meal, especially after carbohydrate consumption.[179] In healthy individuals the incretin effect is responsible for 50% to 70% of the postprandial insulin secretion.[180] In type 2 diabetes, the incretin effect is diminished, mostly because GIP has lost its insulinotropic activity as a result of chronic hyperglycemia.[181,182] Supraphysiologic concentrations of GLP-1 are able to restore glucose-dependent insulin secretion and to normalize plasma glucose in type 2 diabetes, as long as sufficient beta cell mass is still present. It is interesting to note that GLP-1 also inhibits glucagon secretion in a glucose-dependent manner. This effect also contributes to the glucose normalization observed under supraphysiologic GLP-1 plasma concentrations.[183] During the last decade, additional physiologic effects of GLP-1 were discovered that may help to normalize metabolism in type 2 diabetes.[179] GLP-1 also slows gastric emptying and thereby retards the resorption of carbohydrates, and in rodent models it increases beta cell function and beta cell mass. Like other gastrointestinal hormones, GLP-1 is also found as a neurotransmitter in the brain. GLP-1–containing neurons in the hypothalamus are involved in mediating satiety.[184,185] Novel data also describe cardiovascular effects of GLP-1 that seem to be favorable in type 2 diabetes or in patients with the metabolic syndrome (e.g., improvement of left ventricular function in myocardial infarct models, reduction of BP).[186] The incretin-based therapies for type 2 diabetes with GLP-1 receptor agonists or with dipeptidyl peptidase (DPP-4) inhibitors that elevate endogenous GLP-1 plasma concentrations use these GLP-1 effects.[187]

Beta Cell Mass

Several studies have shown that at the time of type 2 diabetes diagnosis, beta cell mass has already decreased to around 50% of the original beta cell mass and that this amount of beta cell reduction is critical.[188–190] With this reduction in beta cell mass, for many middle-aged or old aged persons, normal glucose metabolism is no longer possible. In persons with marked insulin resistance, moderate loss of beta cell mass may already lead to a manifestation of diabetes. Most patients with type 2 diabetes show a 40% to 50% reduction in beta cell mass compared with a nondiabetic age-matched control group.[191–193] The loss of beta cells in comparison with the loss of other cell types within the pancreatic islet is relatively selective for the beta cells; loss of the glucagon-secreting alpha cells or the somatostatin-producing delta cells is not observed in a comparable quantity in type 2 diabetes.[194] Even though the exact causes for the reduced beta cell mass in type 2 diabetes are not completely elucidated, programmed cell death (apoptosis) seems to play a key pathogenetic role. Secondary factors such as elevated free fatty acid plasma concentrations, oxidative stress, and chronic hyperglycemia (see the later discussion of glucose toxicity) lead to an increased rate of beta cell apoptosis. Other possibilities such as a reduced rate of beta cell proliferation or beta cell neogenesis play most likely only a minor role in the reduction of beta cell mass in type 2 diabetes.[191]

Glucose Toxicity

Chronic hyperglycemia leads to a desensitization of the beta cell toward a glucose stimulus. This effect is also described as glucose toxicity of the beta cell. Glucose toxicity does not seem to be a substantial pathogenetic factor for the development of type 2 diabetes or in early stages of the disease. In later stages of diabetes with overt chronic hyperglycemia it may lead to an additional dysfunction of the beta cell contributing to a further decline of metabolic control.[195] It is interesting to note that the results from the United Kingdom Prospective Diabetes Study (UKPDS) showed comparably progressive beta cell dysfunction in the intensively treated patients as well as in the control group.[190] This finding indicates that plasma glucose concentrations may have less influence on the progressive beta cell dysfunction.

Lipotoxicity

Free fatty acids from alimentary sources or from endogenous pools are also involved in mediating beta cell dysfunction. Elevated free fatty acid concentrations lead to a diminished glucose-dependent insulin secretion.[196] Investigations in vitro in beta cell lines showed an increase of programmed cell death (apoptosis) of the cultured cells under the influence of elevated concentrations of free fatty acids. This effect is observed with saturated fatty acids but not with unsaturated fatty acids. An approximately 20-fold–increased apoptosis rate of beta cells was induced by the fatty acids palmitate and stearate, which are predominantly found in fats from animal sources. Fatty acids from plant sources that are monounsaturated or polyunsaturated such as oleate, palmitoleate, and linoleate did not show the apoptotic effect.

Saturated fatty acids most likely transmit apoptotic signals in beta cells via protein kinase C.[197,198] In epidemiologic studies an association between the nutritional fat composition and beta cell function has been suggested. A correlation between the intake of saturated fatty acids and the incidence of type 2 diabetes has been shown.[199,200]

SUMMARY

This chapter gives insight into the pathophysiology and mechanisms involved in insulin resistance, a paramount characteristic of type 2 diabetes.

On the genetic level, SNPs in genes associated with diabetes risk contribute to altered insulin signaling, insulin secretion, organ function, or organ crosstalk (e.g., among the intestine, the endocrine pancreas, the liver, the brain, and the adipose tissue).

The mechanisms involved in insulin resistance mainly occur after insulin binding to the insulin receptor, with insulin normally mediating metabolic effects via the signaling molecules AKT/PKB, as well as mitogenic effects via the signaling proteins Ras/Raf/MAP kinase. In insulin resistance, reduced cellular insulin action is found with respect to metabolic but not mitogenic effects of insulin. Defects in the insulin signaling cascade are already present in the first steps of the signal transmission in insulin resistance and type 2 diabetes.

The activation of the insulin signal transduction cascade leads to glucose transport into the cell. The insulin effect on the glucose transport system is mediated by a translocation of glucose transporters from the intracellular pools to the plasma membrane and activation of these transporters in the plasma membrane. The glucose transporter GLUT-4 plays a major role. A reduced capacity of insulin-dependent translocation of GLUT-4 to the plasma membrane is observed as a consequence of insulin resistance.

Concerning the crosstalk between various tissues, the adipose tissue and adipocytes contribute to the development of insulin resistance by producing and secreting mediators such as adipokines and cytokines that act on the muscle and other target tissues of insulin action. The visceral adipose tissue is now seen as an endocrine organ with respect to special functions concerning the activation and secretion of numerous hormones and cytokines that mediate insulin resistance and chronic inflammation. Chronic inflammation is associated with an increased risk for macrovascular complications in type 2 diabetes and the metabolic syndrome.

Insulin resistance also leads to lipid accumulation in the muscle and liver, aggravating the metabolic disturbances. In NAFLD and NASH, hepatokines such as fetuin-A contribute to insulin resistance and most likely to the increased cardiovascular risk associated with this condition.

The brain has only recently been recognized as an important organ regulating insulin sensitivity. It contributes to energy expenditure and body weight regulation. Neutralizing insulin effects in the brain in animal experiments leads to hyperphagia and obesity and to a reduced peripheral action of insulin in the liver, indicating an important organ interaction between the brain and the liver.

In addition, defects in insulin secretion and pancreatic islet function contribute to the pathophysiology of type 2 diabetes. Multiple defects involving insulin secretion have been characterized in type 2 diabetes. These include a diminished or absent fast insulin response after a sharp rise in glucose concentration (the so-called "first phase" of insulin secretion), an increase in the secretion of proinsulin, a defect in the insulinotropic action of incretin hormones (i.e., a defect in the crosstalk between the small intestine and the endocrine pancreas), and a defect in the interdependent pulsatile secretions of insulin and glucagon. In addition to genetic backgrounds for these pathophysiologic findings (SNPs in diabetes candidate genes), glucotoxicity, lipotoxicity, and the effects of inflammatory cytokines (predominantly secreted by adipocytes) contribute to the defects in pancreatic beta cell function and also loss of beta cell mass in type 2 diabetes.

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3 Type 1 Diabetes

Pathophysiology, Molecular Mechanisms, Genetic Insights

Petter Bjornstad and Marian J. Rewers

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Type 1 diabetes mellitus (T1DM) is one of the most prevalent chronic diseases of childhood, affecting more than 1.4 million people in the United States, of whom 150,000 are children.[1,2] Over the past 50 years, the incidence in children has been increasing at a rapid rate of up to 5% per year worldwide—that is, doubling every 20 years.[3] The lifetime risk of developing T1DM now exceeds 1% in North America and Europe. Whereas T1DM accounts for only approximately 5% of diabetes, it is associated with higher per-person morbidity, mortality, and health care costs than type 2 diabetes (T2DM).[4]

T1DM incidence is trimodal, peaking at the ages of 2, 4 to 6, and 10 to 14 years. This pattern may reflect age-specific infections and increased insulin resistance of puberty. Although children are most visibly affected, half of T1DM patients are diagnosed after age 20. There is generally an equal male-to-female distribution of T1DM; however, a slight male predominance has been reported in high-risk populations, and the opposite in low-risk ethnic groups.[5]

The ongoing pandemic of T1DM cannot be attributed to genetics or increasing survival and fecundity of adults with T1DM; a powerful environmental factor or factors must be at play. In this chapter we review the pathophysiology underlying T1DM, and discuss possible mechanisms linking genetic predisposition to environmental triggers in the development of T1DM.

PATHOGENESIS

T1DM is characterized by a long preclinical period of autoimmune attack on the beta cells, carried out by autoreactive T cells and marked by the emergence of autoantibodies against beta cell autoantigens. The process appears to result from loss of tolerance to beta cell autoantigens in genetically susceptible individuals. Several environmental triggers have been implicated, but none have been definitely proven. **Figure 3-1** illustrates the complexity of the pathogenesis underlying T1DM.

The normal pancreas has a large reserve capacity; at least 70% of the functional capacity of the beta cells must be lost before clinical T1DM develops. Studies of human pancreata in patients with established T1DM suggest that a number of beta cells are able to survive the autoimmune insult, but are unable to secrete sufficient amounts of insulin to prevent hyperglycemia. Rodents may generate new beta cell progenitor cells,[6] but there is no evidence for beta cell regeneration in humans with diabetes.

Selective destruction of pancreatic beta cells results in insulinopenia. The impairment in insulin secretion is also partially functional and caused by the inhibition of insulin secretion by cytokines interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α), TNF-β, and interferon gamma (IFN-γ).[7] Insulin resistance may also play a role in T1DM pathogenesis and cannot be explained simply by obesity or puberty.

After diagnosis, T1DM patients are more insulin resistant than nondiabetic controls despite similar adiposity, body fat composition, and high-density lipoprotein (HDL) cholesterol.[8] Significant insulin resistance has been documented in T1DM patients at or near hemoglobin A1c (HbA1c) targets,[8,9] suggesting that resistance to insulin action on glucose and nonesterified fatty acid suppression are not mediated by prevailing glycemia.[8] In insulin-treated patients, insulin resistance is secondary to prolonged exposure to supraphysiologic levels of exogenous insulin that increase ectopic fat accumulation in liver and skeletal muscles[8] and increase oxidative stress.[10–12] The ectopically accumulated fat and its catabolites are thought to induce insulin resistance via various signaling pathways including mitogen-activated protein kinases (MAPKs), protein kinase C, IκB kinases, S6 kinases, and endoplasmic reticulum stress.[13–15] Chronic insulin resistance increases the risk of diabetic macrovascular and microvascular complications.[8,16–18a]

AUTOIMMUNITY

The nonobese diabetic (NOD) strain of mouse is an essential model of autoimmune T1DM. The advantage of this murine strain is that it develops spontaneous autoimmune diabetes, which shares many similarities with autoimmune type 1 diabetes in human patients. Recent research on this model has provided a wealth of insight into mechanisms likely involved in pathogenesis of T1DM.[19,20]

It is now generally accepted that T1DM arises from a breakdown in self-tolerance to beta cell autoantigens. Chronic T cell–mediated inflammation of the islets results in selective destruction of beta cells and sparing of the alpha, delta, and pancreatic polypeptide cells.[21] Alternative scenarios are possible—for example, an adaptive immune response to persistent infection of the islets where beta cells are particularly sensitive to cytokine IL-1β–mediated killing, and increased expression of class I molecules during local infections may enhance their susceptibility.[22,23]

Autopsy data have shown that destruction is caused by infiltration of the islets by macrophages, dendritic cells, natural

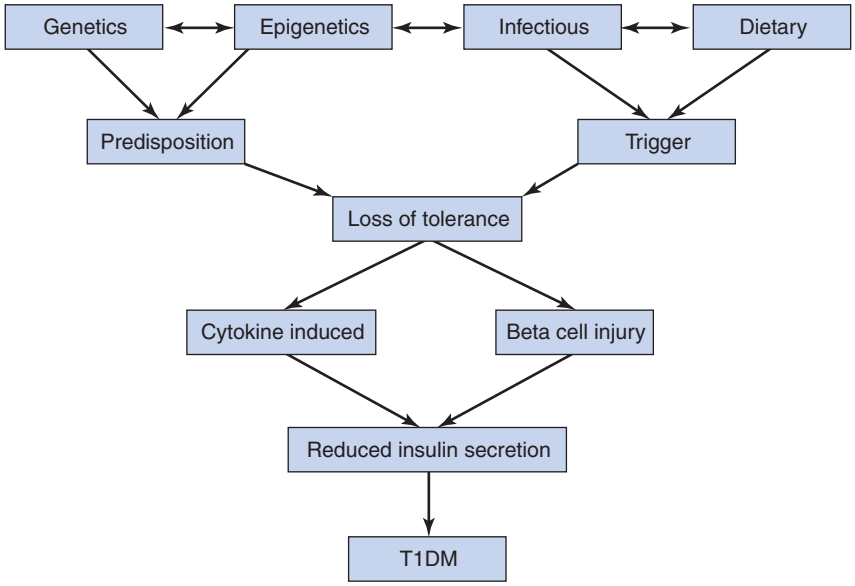


FIGURE 3-1 Diagram showing the complexity of the pathogenesis of type 1 diabetes mellitus (T1DM).

killer cells, and lymphocytes.[24] The T cells are the key players in the autoimmune attack of beta cells, including helper T cells, cytotoxic T cells, and regulatory T cells.[25] Humoral response and autoantibody production do not cause direct beta cell damage, but develop secondary to beta cell damage, and are useful disease markers.

Loss of Tolerance

Immune tolerance is essential to achieve immune homeostasis and self-tolerance. The loss of self-tolerance is the hallmark of T1DM pathogenesis. The establishment of tolerance starts in fetal life and includes both a central and a peripheral arm. Central tolerance is the process whereby immature T and β cells acquire tolerance to self-antigens during maturation within the thymus and bone marrow, respectively. It consists of positive and negative selection. Positive selection is the process of testing T cells for major histocompatibility complex (MHC) restriction. T cells with receptors with weak binding to MHC class I and II are allowed to survive (positively selected). This process is important in that it sets up a system in which all mature T cells will have T cell receptors (TCRs) that recognize antigens presented by MHC. Negative selection is the process whereby T cells that bind with high affinity to MHC class I and II, alone or carrying self-peptides, are eliminated by apoptosis. For central tolerance to be efficient, the negatively selecting stromal elements in the thymus medulla will have to express a large diversity of tissue-restricted antigens (TRAs) that represent as many self-antigens expressed outside of the thymus as necessary to establish and maintain self-tolerance. This is possible by promiscuous gene expression, which is the expression of a highly diverse set of genes in the medullary thymic epithelial cells, otherwise expressed in a strictly tissue-restricted fashion. Except for the involvement of the autoimmune regulator (AIRE), the molecular and cellular regulation of this gene expression pattern is poorly understood. The absence of a single TRA is sufficient to elicit spontaneous autoimmunity.[26]

Under this model, thymus dysfunction could lead to a decrease in the expression of T1DM-related antigens promoting a continuous enrichment of the peripheral T cell repertoire with self-reactive T cells, as well as a decrease in the selection of specific T regulatory cells (Tregs). Thymus transplantation from diabetes-resistant to diabetes-prone rats can prevent insulitis and diabetes; conversely, transplantation of thymus from nonobese diabetic to diabetes-resistant mice induced insulitis.[27,28] All the members of the insulin gene family are expressed in the thymus.[29] In mice, in which two genes code for (pro)insulin (*Ins1* and *Ins2*), *Ins2* is predominantly expressed in the thymus, whereas *Ins1* is dominant in the islet beta cells, which leads to a higher immune tolerance to *Ins2*. $Ins2^{-/-}$ cogenic NOD mice have a significantly higher rate of insulitis and diabetes than $Ins1^{-/-}$ cogenic NOD mice.[30,31]

Negative thymic selection is not entirely efficient and inadvertently permits the efflux of some autoreactive T cells with low-affinity TCR for self-antigens. To avoid the development of autoimmunity, additional mechanisms are in place. One of these mechanisms is the thymic generation of Tregs, which maintain homeostasis of the immune system and tolerance to self-antigens by controlling self-reactive T cells. The depletion of naturally occurring Tregs elicits multiorgan autoimmune disease, for example, the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome—a rare congenital deficiency of forkhead box P3 (FOXP3) expression in humans.[32] Tregs constitute 10% of $CD4^+$ T cells in the thymus and the periphery and express the IL-2 receptor alpha chain (CD25) and FOXP3 protein.[33] They are initially anergic, but when activated they suppress proliferation and IL-2 production of naïve and memory T cells.[34]

Another mechanism allowing peripheral tolerance to self-antigens involves anergy. When a self-reactive lymphocyte recognizes its cognate antigen on a cell but does not receive the required co-stimulatory signal, it becomes anergized. The cell-surface glycoproteins CD80 (B7-1) and CD86 (B7-2) are essential co-stimulatory molecules, found almost exclusively on professional antigen-presenting cells (APCs). Interaction of these B7 molecules on APCs with CD28 on T cells is required for T cell activation. Moreover, if naïve T cells do become activated, they express an additional

receptor called *cytotoxic T lymphocyte–associated 4* (CTLA-4), which has a greater binding affinity for the B7 molecules than CD28.[35] Binding of CTLA-4 to B7 results in a negative signal to the T cells, resulting in inhibition of T cell activity.[36] CTLA-4 is also an important co-stimulatory molecule expressed by T-regulatory cells.[37]

β cell tolerance occurs as a result of clonal deletion through apoptosis of immature β cells reactive to self-antigens. Immature β cells expressing surface IgM that reacts with self-antigens are rendered unresponsive or anergic. Thus, only those β cells that do not react with self-antigens in the bone marrow are allowed to mature and migrate to the periphery where further maturation occurs.

Autoantigens

Several autoantigens have been identified in T1DM and may play an important role in the initiation and progression of the autoimmune injury (**Table 3-1**). Most of the autoantigens are human leukocyte antigen (HLA) A2 restricted, $CD8^+$ T cell epitopes such as proinsulin, glutamic acid decarboxylase (GAD), islet-specific glucose-6-phosphatase catalytic subunit–related protein (IGRP), and islet amyloid polypeptide (IAPP).[38,39] The study of antigens in the development of T1DM is more complicated than initially thought and includes the following concepts: (1) intermolecular spreading of antigenicity; (2) tissue-specific cleavage producing antigenic peptides specific to beta cells; and (3) synergy of multiple islet antigens.

TABLE 3-1 Autoantigens and Autoantibodies

AUTOANTIGEN	DESCRIPTION OF ANTIGEN	ANTIBODY
Insulin	Protein secreted by β cells	IAA
Glutamic acid decarboxylase	Enzyme catalyzing decarboxylation of glutamate to GABA	GADA
Insulinoma-associated protein 2	Neuroendocrine protein	IA-2A
Islet-specific glucose-6-phosphatase catalytic subunit–related protein	Catalytic subunit of glucose-6-phosphatase	IGRPA
Chromogranin A	Protein found in secretory granules in β cells	ChgAA
Zinc transporter 8	β cell–specific cation efflux zinc transporter	ZnT8A

GABA = γ-aminobutyric acid.

With regard to intermolecular spreading of antigenicity, we know that the initial antibody response in T1DM occurs primarily against insulin or GAD, spreading over time to other antigens. Tissue-specific cleavage appears critical to generation of diabetogenic autoantigens. A good example is the cleavage product of chromogranin A (ChgA)—WE-14, which is specifically recognized by the pathogenic BDC2.5 TCR (see later). It may also be necessary for T cells to target multiple beta cell antigens for the development of T1DM to occur (synergy of multiple antigens). For example, the targeting of IGRP by the $CD8^+$ T cells is very diabetogenic, but only in the context of the T cells also targeting insulin peptide B:9-23.[40]

Insulin

Insulin is composed of two peptide chains referred to as the A chain and B chain, which are linked together by two disulfide bonds, and an additional disulfide is formed within the A chain. The A chain consists of 21 amino acids, and the B chain of 30 amino acids. Proinsulin is the prohormone precursor to insulin. C peptide, a 31–amino acid peptide, is cleaved from proinsulin as it is enzymatically converted to insulin. One current leading hypothesis is that insulin itself may be the crucial autoantigen in T1DM. In NOD mice, a single amino acid mutation of insulin peptide 9-23 prevents development of diabetes.[41] Recently, NOD studies have also shown that *only* APCs from islets are able to stimulate anti-B:9-23 T cells.[42] Furthermore, knockouts of the insulin genes in NOD mice greatly influence progression to disease.[31] In addition, the administration of insulin or its B chain can prevent or delay diabetes in susceptible mice during the prediabetic phase. Prospective studies, including the German BABYDIAB and the Finnish Diabetes Prediction and Prevention Study (DIPP), also indicate that autoantibodies against insulin usually emerge before any other antibodies, including anti-GAD65, anti–IA-2, and anti–zinc transporter 8 (ZnT8) (**Table 3-2**).[43–45]

It is astonishing that proinsulin, a protein of only 86 amino acids, contains so many epitopes for a spectrum of HLA class I and class II alleles. T cell reacting epitopes have been demonstrated within insulin A and B chains,[46,47] the C peptide and B-C chain junction, and the C-A chain junction region.[48] Specific $CD4^+$ and $CD8^+$ T cells targeting insulin and precursor epitopes has been reported both in newly diagnosed and in chronic T1DM.[49] $CD4^+$ T cell reactivity has been noted mostly in connection with susceptibility alleles HLA-DR3 and HLA-DR4.[50] $CD8^+$ T cell reactivity, on the other hand, is associated in particular with HLA-A2.[39]

TABLE 3-2 Prospective Cohort Studies of the Natural History of Type 1 Diabetes

	BABYDIAB (GERMANY)	DAISY (COLORADO)	DIPP (FINLAND)	TEDDY (FOUR COUNTRIES)
Year started	1989	1993	1994	2004
First-degree relatives *(n)*	1650 offspring	1120 offspring siblings	8150	923
General population *(n)*	–	1422		7754
Persistent islet Ab+ *(n)*	149	183	537	450*
Diabetes (*n*)	47	71	320	126†

Note: The BABYDIAB consists of offspring of parents with T1DM. DAISY has two groups: first-degree relatives of T1DM and high-risk individuals from the general population. DIPP screened infants in the general population, including first-degree relatives, for HLA types. Finally, the TEDDY cohort consists of newborns with a first-degree relative with T1DM as well as those from the general population enrolled from six clinical centers in four countries (personal communication from Ziegler, Simell, and Rewers, October 2011).

*As of October 2012, 800 cases expected by 15 years of follow-up.

†As of October 2012, 400 cases expected by 15 years of follow-up.

Ab+ = Autoantibody positive.

Glutamic Acid Decarboxylase

GAD is an enzyme that catalyzes the decarboxylation of glutamate to γ-aminobutyric acid (GABA) and CO_2. GAD isoforms GAD67 and GAD65 are encoded by two different genes, *GAD1* and *GAD2*. *GAD2* is expressed in the pancreas and the brain. The association of GAD65 autoantibodies with T1DM is well known,[51,52] and these autoantibodies were found in 52% of newly diagnosed children in the U.S. SEARCH for Diabetes in Youth study.[53] More recently, GAD has been used as a tolerogenic vaccine to preserve functional beta cells. Unfortunately, GAD65 antigen therapy did not significantly improve clinical outcomes over a 15-month period in a recent randomized controlled trial (RCT).[54]

Insulinoma-Associated Protein 2

Insulinoma-associated protein 2 (IA-2) is a neuroendocrine protein and a member of the tyrosine phosphatase family, with its gene located on chromosome 14.[55] Antibodies against IA-2 appear later than antibodies against insulin or GAD and are associated with progression to diabetes. Ellis and coworkers found anti–IA-2 antibodies in the sera of 58% of newly diagnosed T1DM patients[55]; and, similarly, Dabelea and colleagues identified IA-2A in 60% of newly diagnosed children in the SEARCH cohort.[53]

ZnT8

ZnT8 is a novel autoantigen in T1DM.[56] It is a beta cell–specific cation efflux zinc transporter with its gene located on chromosome 8. The Diabetes Autoimmunity Study in the Young (DAISY) cohort consists of two groups, including first-degree relatives of individuals with T1DM and individuals from the general population who underwent HLA typing of cord blood, and has shown that ZnT8 antibodies are present in 60% to 80% of newly diagnosed T1DM patients (see **Table 3-2**).[57] In addition, 25% of T1DM patients who are negative for autoantibodies to insulin, GAD, IA-2, and islet cells (ICA) tested positive for ZnT8 autoantibodies.[57] Moreover, the DAISY study showed that ZnT8 autoantibodies emerge later than the other insulin autoantibodies.[57] The antibodies have also been shown to decline quickly after diagnosis of T1DM.[58] Howson and colleagues found an association between anti-ZnT8 antibodies and the single-nucleotide polymorphisms (SNPs) rs7522061 and rs9258750A > G in, respectively, the Fc-receptor-like–3 *(FCRL3)* gene and HLA class I locus.[58]

Islet-Specific Glucose-6-Phosphatase Catalytic Subunit–Related Protein

IGRP is an important autoantigen that is selectively expressed in beta cells.[59] IGRP is recognized as an antigen by the $CD8^+$ T cell clone NY8.3.[59] IGRP is not expressed in the thymus in NOD mice, thereby allowing IGRP-reactive T cells to escape into the periphery. For this reason, peripheral tolerance independently confers protection against autoimmunity.[60,61] Krishnamurthy and colleagues successfully showed that peripheral tolerance alone is sufficient to protect NOD8.3 mice from autoimmune diabetes.[62]

Chromogranin A

The chromogranin A (ChgA) gene is located on chromosome 14 and encodes a protein found in secretory granules of many different secretory cell types, including beta cells. It is a precursor pro-protein that is proteolytically processed within the granule to form a variety of peptides, including vasostatin 1 (VS-1; ChgA 1-76, ChgA 29-42), VS-2 (ChgA 1-113), and WE-14 (ChgA 358-371). The functions of these peptides are still not clearly understood. As previously mentioned, ChgA illustrates the importance of tissue-specific cleavage. In fact, a specific cleave of ChgA within the beta cells is essential for T cell binding. The cleavage product WE-14 is tissue-specific, meaning it is specifically produced in the islet cells and recognized by pathogenic BDC2.5 TCR of NOD mice via pockets 5 through 9 of the I-Ag7 MHC class II molecule.[63] Nikoopour and colleagues identified another cleavage product, ChgA 29-42 peptide, as the natural epitope of BDC2.5 $CD4^+$ T cells, and demonstrated induction of diabetes after transfer of ChgA 29-42 activated BDC2.5 splenocytes into NOD/severe combined immunodeficiency (SCID) mice.[64]

In contrast, cells expressing noncleaved ChgA do not effectively produce these autoantigenic peptides and are thus not recognized by T cells. For example, production of WE-4 cleaves four N-terminal amino acids that, if present, would occupy pockets 1 to 4 on the I-Ag7 cMHC class II molecule and thereby block BDC2.5 TCR stimulation.[63]

Adaptive Immune Response

T Cell Response

The development of the destructive pathologic lesion known as *insulitis,* and the steps leading to T1DM in humans, are only partially understood. Immunohistologic examination of pancreatic tissues from patients with T1DM has demonstrated that in contrast to the animal models of spontaneous T1DM, insulitis is rare in humans.[65] When present, anti-islet T-lymphocytes, both $CD4^+$ and $CD8^+$ T cells, beta cells, macrophages, and dendritic cells are found in the inflammatory lesion.[66] $CD8^+$ T lymphocytes represent the largest cell population within the inflammatory infiltrates and are widely recognized as the final effectors in the pathogenesis of T1DM.[25,67] Immunosuppressive drugs specifically directed against T cells delay disease progress,[68] and transfer of anti-islet specific $CD4^+$ and $CD8^+$ T cells can induce diabetes in immune-incompetent recipient NOD mice.[69]

Mechanistic studies involving $CD8^+$ T cell (CTL) killing of human islets have shown that interferons can accelerate human islet killing by inducing expression of MHC class I molecules on beta cells[70] and thereby targeting them for cytotoxic T cell destruction.[71,72] Killing of human islets is shown to be perforin dependent in the absence of cytokines.[73] Further studies have also shown that CTL-mediated killing occurs via caspase-independent pathways in human T1DM.[73] CTLs are also sources of reactive oxygen species (ROSs) and proinflammatory cytokines. Because beta cells have a low capacity for disposing of ROSs generated from mitochondrial metabolism compared with other tissues,[74,75] ROSs could act as soluble mediators of beta cell death in T1DM.[76] $CD4^+$ T cells, on the other hand, recognize peptides presented by MHC class II molecules and participate in the destruction of beta cells directly by the production of cytokines, and indirectly by the activation of local innate cells, such as macrophages and dendritic cells.[77] T cell–derived cytotoxicity in mouse models occurs via nitric oxide (NO)–dependent necrosis with very little contribution from apoptosis.[78] Conversely, in humans, preventing inducible NO synthase function does not consistently prevent beta cell destruction.[79] There is also evidence that apoptosis is an important pathway of cytolysis.[80]

Mitochondria in beta cells are essential for several cellular processes, including glucose-stimulated insulin secretion. These organelles are also important regulators of cell death. TNF-α– and IFN-γ–induced cell death depends on functional mitochondria, evident by the mitochondrial DNA (mtDNA)–deficient cells being resistant to cytokine killing.[81,82] Apoptosis is also a very energy-demanding process, and it is hypothesized that inhibition of adenosine triphosphate (ATP) production by endogenous inhibitors of oxidative phosphorylation may cause the switch from apoptosis to necrosis in metabolically suppressed cells (i.e., beta cells pre-T1DM) that have already been signaled for apoptotic cell death. In addition, mitochondria are an important source of cellular ROSs that can lead to caspase-dependent apoptosis in beta cells.[83]

Endoplasmic reticulum is also an organelle that is essential in the normal beta cell physiology. Beta cells are very prone to endoplasmic reticulum stress, as evidenced by the many mutations that affect insulin protein folding. The additional viral protein synthesis in a virally infected beta cell may cause endoplasmic reticulum stress that would not only saturate the cell's ability to replenish stored insulin pools, but also make it vulnerable to apoptosis and direct T cell lysis.[84]

Cytokines

Cytokines play an essential role in the pathogenesis of T1DM, and IFN-γ, TNF-α, and IL-1β have been particularly well studied. Immunohistologic samples from patients with T1DM demonstrate IFN-γ–secreting lymphocytes in the islets.[85] TNF-α– and IL-β–producing macrophages and dendritic cells have been identified in pancreatic islets in patients with recent-onset T1DM.[86] Human islets have been shown to be particularly sensitive to combinations of IL-1β, TNF-α, and IFN-γ. For example, addition of TNF-α to human islets inhibits beta cell function and, when combined with IFN-γ, causes reduced beta cell viability.[87] Cytokines have also been implicated in determining whether the immune response of $CD4^+$ T cells to an antigen is predominantly cellular (Th1) or humoral (Th2). T1DM is believed to be a Th-1 associated disease. Cytokines not only are able to control the type of immune response mounted, but also alter the expression of many proteins in the beta cells, including insulin. IFN-γ stimulates the expression of MHC class I molecules in islet beta cells, which is illustrated well by the prevention of insulitis in NOD mice after treatment with antibodies to IFN-γ.[88] IL-1 stimulates the expression of protective proteins including ganglioside and superoxide dismutase, both thought to be involved in the recovery of beta cell injury.[89] It has also recently become apparent that insulinopenia in T1DM is not solely a result of beta cell destruction, but also is secondary to a reversible beta cell dysfunction caused by inflammatory cytokines.

Antibody Response

Autoantibodies could theoretically injure beta cells by antibody-dependent complement cytotoxicity or by targeting NK cells to beta cell antigens, but induction of T1DM in animal models has been shown to be dependent on T cells.[90] Consequently the pathogenic significance of T1DM-related antibodies is very low, and the real effectors of beta cell autoimmune destruction are self-reactive $CD4^+$ and $CD8^+$ T cells.[68]

Extending these observations to the clinical context, even though antibodies are not required for the development T1DM, they are valuable prognostic markers for disease risk. The fact that autoantibodies also appear several years before the clinical onset of T1DM when insulin secretion is normal also makes them very useful in predicting the window of opportunity to potentially prevent the disease in the future.[91] As they are also the most reliable diagnostic test, testing for autoantibodies is now an essential part of the T1DM workup. In the Childhood Diabetes in Finland (DiMe) study, a prospectively family study in Finland in which serum samples were obtained at the diagnosis of T1DM from probands and siblings, 91% of 758 children and adolescents younger than 15 years with newly diagnosed T1DM tested positive for at least two antibodies, and 71% for three or more.[92]

More recently, in the multicenter SEARCH for Diabetes in Youth study, 74% of 2291 newly diagnosed cases of diabetes in patients younger than 20 years showed autoantibody positivity (positive for either glutamic acid decarboxylase antibodies [GADA] or insulinoma associated-2 autoantibodies [IA-2A]).[53] Wenzlau and colleagues showed that by testing for circulating antibodies to ZnT8A in combination with the three other antibodies (GADA, IA-2A, and IAA), one is able to detect up to 98% of individuals at disease onset.[57]

Human studies have demonstrated an important role of B lymphocytes as APCs in T1DM.[93] In addition, β cell deficiency by gene targeting and β cell depletion by specific antibodies have been shown to prevent the development of T1DM in NOD mice.[94]

Innate Immune System Response

There is growing evidence that the innate immune system also plays an important role in the pathogenesis of T1DM, conferring protection in the early stages, and is later involved in precipitating the disease (**Table 3-3**).

Macrophages, in particular, have shown to be important contributors in the pathogenesis of T1DM. Preventing the influx of macrophages into the pancreas of NOD mice has been shown to abort the induction of T1DM.[95,96] Macrophages in NOD mice function differently than in non-obese resistant (NOR) mice, with regard to both cytokine production and phagocytosis, producing higher levels of proinflammatory IL-12, IL-1β, and TNF-α cytokines[86,97] and demonstrating impaired phagocytosis of apoptotic beta cells.[98]

TABLE 3-3 Innate Immune Cells

TYPE OF CELL	ROLE IN T1DM PATHOGENESIS	REFERENCE
Macrophages	Producing proinflammatory cytokines and impaired phagocytosis of apoptotic β cells	86, 95–98
Dendritic cells	Peripheral immune tolerance by inducing expansion of Treg cells	99, 100
Plasmacytoid dendritic cells	Conversion of naïve $CD4^+$ T cells to Treg cells	103
Natural killer cells	Inverse relation with Treg cells and associated with coxsackievirus B infection	105, 107, 108
Invariant natural killer cells	Recognize glycolipid antigens, and induction of these cells has shown to protect against T1DM development in NOD mice	109, 110, 111

Dendritic cells are implicated as important contributors to peripheral immune tolerance[99] by being able to induce expansion of Tregs.[100] Studies in NOD mice have shown that induction of dendritic cells with granulocyte colony-stimulating factor (G-CSF) expands Treg cells and thereby suppresses beta cell autoimmunity.[101] The plasmacytoid subpopulation of dendritic cells has a protective role in the pathogenesis of T1DM.[102] Plasmacytoid dendritic cells have specifically been implicated in the conversion of naïve $CD4^+$ T cells to Treg cells, which are key contributors to ensuring peripheral immune tolerance and preventing T1DM.[103]

Natural killer cells are also implicated in the pathogenesis of T1DM and have been detected in the pancreases of NOD mice and in the pancreases of patients with T1DM.[104] Again, their role in T1DM pathogenesis is complex; studies have shown both a protective and a deleterious role of these innate cells. Impaired natural killer cell function has been documented in lymphoid tissues of NOD mice.[105] Conversely, the depletion of Treg cells in NOD mice is associated with an exacerbation of natural killer cell activation in the pancreas and is concomitant with disease onset.[106] The presence of natural killer cells in the pancreas of T1DM patients has also been associated with coxsackievirus B infection.[107,108] Furthermore, natural killer cells are thought to be key cellular players in the pathogenesis of T1DM induced by coxsackievirus infection in mouse models.[107,108]

An unusual subpopulation of natural killer cells that has also been implicated in the pathogenesis of T1DM is the invariant natural killer T cells. This is a group of T cells that recognizes glycolipid antigens presented by the HLA class I–related CD1d molecule. These T cells play a regulatory role in the immune system, and many studies have demonstrated their protective role against T1DM.[109,110] Induction of invariant natural killer T cells by glycolipids (e.g., α-galactosylceramide) may prevent T1DM development in NOD mice.[111]

ETIOLOGY

The cause of immune susceptibility in the pathogenesis of T1DM is still unknown, but it is very likely that both genetic and environmental factors are essential contributors to the autoimmune destruction of pancreatic beta cells.

Genetics

T1DM is a polygenic disease that does not fit any mendelian pattern of inheritance. This is exemplified well by the fact that siblings of patients with T1DM have a 15-fold greater risk of developing T1DM compared with the general population, and the concordance rate for T1DM in monozygotic twins is greater than 50%, compared with 6% to 10% concordance in dizygotic twins.[112] Susceptibility and protective genes have been identified at more than 40 loci. Carrying a susceptibility gene increases the risk for T1DM, but does not automatically imply that the person will develop the disease. By far the most important T1DM risk genes are found in the HLA region located on chromosome 6p21. This locus accounts for up to 30% to 65% of genetic T1DM susceptibility.[113] Non-HLA T1DM loci have a smaller but important effect on T1DM susceptibility; most appear to primarily affect the immune system and particularly T cells.[114]

TABLE 3-4 HLA Genes

HLA GENE	SUBTYPES	ROLE IN T1DM PATHOGENESIS	REFERENCE
HLA I	HLA-A, HLA-B, HLA-C	Expressed on all nucleated cells, permitting $CD8^+$ T cell recognition	118
HLA II	HLA-DR, HLA-DQ, HLA-DP	Expressed exclusively on professional antigen-presenting cells capable of activating $CD4^+$ T lymphocytes	113, 116, 117
HLA III		Not directly involved in antigen presentation, but important components of the immune system	120

HLA Genes

The major histocompatibility (HLA) genes make up cell-surface proteins involved in antigen presentation (**Table 3-4**). They are also among the most polymorphic in the human genome, which confers a heterozygous advantage allowing the presentation of a larger variety of antigens to the immune system and thus providing greater protection from new pathogens. HLA class II molecules (HLA-DR, HLA-DQ, and HLA-DP) are expressed exclusively on B lymphocytes, dendritic cells, and macrophages—professional APCs capable of activating $CD4^+$ T lymphocytes. In contrast, HLA class I molecules (HLA-A, HLA-B, and HLA-C) are expressed on all nucleated cells, permitting $CD8^+$ (cytolytic) T cell recognition. HLA class III proteins are not directly involved in antigen presentation, but still make up important components of the immune system.

Diabetes susceptibility is related to peptide-binding characteristics of the various HLA gene products, but exactly how HLA molecules confer susceptibility to selective autoimmune-mediated beta cell destruction is unknown. One possible explanation is that susceptibility-conferring HLA molecules initiate autoimmunity by binding diabetogenic self-antigens and presenting them efficiently to T lymphocytes. In contrast, protective HLA molecules would bind these peptides and present them to the immune system less efficiently. Another, more plausible alternative is that poor binding and presentation of self-antigens (e.g., preproinsulin, GAD, IA-2A, and ZnT8) in the thymus results in an ineffective central tolerance of diabetogenic self-antigens and thus breakdown of self-tolerance.[114]

T1DM is most strongly associated with the polymorphisms of six of the genes of the HLA class II locus IDDM1: HLA-DRB1, HLA-DRA1, HLA-DQB1, HLA-DQA1, HLA-DPB1, and HLA-DPA1. Specific combinations of these alleles are associated with a spectrum from highly susceptible to highly protective genotypes. The highest risk genotype, HLA-DR3, DQB1*0201/DR4,DQB1*0302, is present in 2.4% of the general population and 25% to 40% of T1DM patients, and is associated with an earlier onset of T1DM. The risk of developing T1DM with this genotype is approximately 1 in 15, compared with a risk of 1 in 300 in the general population.[115] The next highest-risk genotypes are those homozygous for polymorphisms in DR4 or DR3. At least one of the two highest-risk haplotypes—DR3-DQA1*0501-DQB1*0201 and DR4-DQA1*0301-DQB1*0302—is present in more than 90% of patients with T1DM.[113,116] On the other hand, the HLA-DQA1*0102 and DQB1*0602 alleles confer protection from T1DM.[117]

HLA class I genes also include both susceptibility and protective alleles. The HLA-B*39 allele is associated with progression to T1DM in children positive for either one or two autoantibodies.[118] HLA-A*24 is associated with more aggressive islet destruction, and conversely HLA-A*03 and HLA-A*11 appear to confer protection against T1DM development.[118] Overexpression of HLA class I molecules by the beta cells is thought to be an important event preceding insulitis.[119]

The HLA class III region comprises gene products involved in the activation cascades of the complement system, hormonal synthesis, inflammation, cell stress, extracellular matrix organization, and immunoglobulin superfamily members.[120] Polymorphisms in the *AIF-1* gene have been shown to be significantly associated with T1DM susceptibility after conditioning on HLA-DRB1, HLA-DQB1, HLA-A, and HLA-B alleles.[121]

Non-HLA Genes

Despite being the most significant genetic locus in T1DM, HLA alleles cannot account for the entire genetic predisposition of this disease. The fact that T1DM has increased by approximately 3% per year worldwide over the past three decades,[122] despite a decrease in patients with the high-risk HLA-DR3/4 genotype, suggests the importance of non-HLA–related alleles and other environmental factors in T1DM pathogenesis.[123] Numerous non-HLA genes have been identified to be associated with T1DM risk; the most extensively investigated include insulin gene *(INS)*, cytotoxic T lymphocyte–associated 4 gene *(CTLA-4)*, protein tyrosine phosphatase nonreceptor type 22 gene *(PTPN22)*, and IL-2 receptor alpha gene *(IL2RA)* (**Table 3-5**).

Insulin Gene

Insulin-dependent diabetes mellitus 2 (IDDM2) represents a genetic susceptibility locus for T1DM within *INS*, which is located on chromosome 11p15.5, and accounts for 10% of familial clustering.[124] The genetic risk conferred by mutations within the insulin gene is a result of its role as a primary initiating autoantigen in T1DM.[125,126]

The *INS* gene is transcribed and translated in the thymus, which is essential for central immunologic tolerance. The IDDM2 locus gives rise to a variable number of tandem repeats (VNTR) at the promoter end of *INS*. The number of repeats ranges from 25 to approximately 200, and the alleles of the proinsulin gene are classified by total size. Type I insulin VNTR consists of 26 to 63 repeats, type II of 64 to 140, and type III of 141 to 209.[127,128] The number of VNTRs appears to correlate with the risk for developing T1DM. For that reason, type I confers susceptibility; patients homozygous for type I have lower levels of insulin expression in the thymus[125,126] and higher titers of insulin autoantibodies.[129] Conversely, VNTR type III protects carriers from T1DM.[125,126] The mechanistic explanation is that VNTRs regulate the expression of insulin in the thymus by affecting the AIRE, a transcription factor, binding to its promoter region.[130] Type I VNTRs will induce lower transcription of insulin in the thymus, where central tolerance to autoantigens operates, resulting in reduced tolerance—that is, less efficient elimination by negative selection of insulin-reactive T cells, and increased risk of T1DM development.

Cytotoxic T Lymphocyte–Associated Protein 4 Gene

The *CTLA-4* gene is located on chromosome 2q33, and its polymorphisms have been shown to contribute to T1DM susceptibility.[131] The CTLA-4–encoded molecule is a costimulatory receptor involved in the IL-2 receptor signaling pathway and plays an important role in the regulation of peripheral tolerance.[132] It is expressed by Tregs and functions as a negative regulator of T cell activation; binding of CTLA-4 to B7 results in inhibition of T cell activity.[133] In particular, variations in the concentrations of soluble CTLA-4 protein and the +49 G/G polymorphism have been associated with T1DM risk.[134]

Protein Tyrosine Phosphatase Nonreceptor Type 22 Gene

The protein tyrosine phosphatase nonreceptor type 22 *(PTPN22)* gene is located on chromosome 1p13[135] and is strongly associated with T1DM as well as other autoimmune diseases.[135] The *PTPN22* gene encodes the lymphoid-specific protein tyrosine phosphatase (LYP), which inhibits T cell activation by dephosphorylating essential kinases in T cell signaling, including lymphocyte-specific protein tyrosine kinase (LCK) and zeta-chain-associated protein kinase 70 (ZAP70).[114] There is a strong association between polymorphisms of the *PTPN22* gene and T1DM risk.[136] The 1858 T variant is also independently associated with the development of persistent islet autoimmunity among individuals with the high-risk HLA genotype for T1DM.[137] The 1858 T variant results in a missense mutation, R620W, which causes gain of function.[138] This variant of PTPN22 is unable to bind the signaling molecule Csk, allowing the accumulation of large numbers of self-reactive T cells and contributing to autoimmunity.

Interferon Induced with Helicase C Domain 1 Gene

The interferon induced with helicase C domain 1 *(IFIH1)* gene is located on chromosome 2q and has been associated with T1DM in genome-wide association studies.[139] A possible mechanism explaining T1DM susceptibility is that the cytoplasmic helicase senses and initiates antiviral activity against picornaviruses by increasing interferon production and class I HLA expression.[140] This increased expression enables the cytotoxic $CD8^+$ T cells to recognize both

TABLE 3-5 Non-HLA Genes

HLA GENE	LOCATION	ROLE IN T1DM PATHOGENESIS	REFERENCE
Insulin gene *(INS)*	Chromosome 11p15.5	Primary initiating autoantigen in T1DM	124, 125, 126
Cytotoxic T lymphocyte–associated protein 4 gene *(CTLA4)*	Chromosome 2q33	Polymorphisms shown to contribute to T1DM susceptibility because of its role in regulation of peripheral tolerance	131, 132
Protein tyrosine phosphatase nonreceptor type 22 gene *(PTPN22)*	Chromosome 1p13	Strongly associated with T1DM and other autoimmune diseases	135
Interferon induced with helicase C domain 1 gene *(IFIH1)*	Chromosome 2q	Associated with T1DM in genome-wide association studies	139
Interleukin 2 receptor alpha subunit gene *(IL2RA)*	Chromosome 10p15.1	Implicated in several autoimmune diseases, including T1DM	142

viral and beta cell antigens, which may result in beta cell apoptosis.[141]

Interleukin 2 Receptor Alpha Subunit Gene

The *IL2RA* gene is located on chromosome 10p15.1.[142] This gene encodes the expression of CD25 on regulatory and memory T cells and is implicated in a number of autoimmune disorders, including T1DM.[142] The expression of CD25 is important for suppressing T cell proliferation, and unregulated expression may cause uninhibited T cell proliferation and predispose to autoimmunity.[143] Both a susceptible (SS) and a protective (P1P1) haplotype for *IL2RA* have been identified, and recent studies have shown that the SS haplotype is associated with decreased IL-2 responsiveness and FOXP3 expression by Tregs, both important in modulating self-tolerance.[144]

Epigenetics

Epigenetics refers to modifications to the genome that do not involve a change in the actual nucleotide sequence. The most common mechanisms include DNA methylation and chromatin remodeling. Uniparental disomy (imprinting) is an example of epigenetics in which there is silencing of either the maternal or the paternal allele at one or more genetic loci. Offspring of affected fathers have a 6% to 7% risk of developing T1DM, more than double that of affected mothers,[145] suggesting an imprinting effect. Epigenetics is increasingly recognized as a possible molecular mechanism for gene-environment interactions. Miao and colleagues found that CTLA-4 had a different H3K9me2 methylation pattern in T1DM lymphocytes versus normal.[146] They also noted significant variations in histone H3K9Ac levels at the promoter regions of *HLA-DRB1* and *HLA-DQB1* genes in monocytes between T1DM patients and healthy controls.[147] Fradin and colleagues found consistent methylation differences between T1DM patients and nondiabetic controls at CpG sites at the proximal part of the *INS* gene promoter.[148] The fact that epigenetics is implicated in immune tolerance was recently illustrated by Bettini and colleagues. Their study showed that epigenetic modifications of *FOXP3* resulted in abnormal Treg function, Treg cell insufficiency, and rapid acceleration of diabetes in a murine model.[149]

Environmental Factors

It is well accepted that environmental factors play an important role in the pathogenesis of T1DM. The potential mechanisms include direct beta cell toxicity, the triggering of beta cell autoimmunity, molecular mimicry, and induction of insulin resistance. The Environmental Determinants of Diabetes in the Young (TEDDY) study, a large multicenter study, is currently under way to identify environmental factors predisposing to or protective against islet autoimmunity and T1DM and will, it is hoped, add insight into both dietary and infectious triggers.[150]

Dietary Factors

Islet autoantibodies start emerging during the first year of life, suggesting that early life exposure(s) may be pivotal.[45] Consequently, infant and childhood dietary factors have been implicated as a vehicle of environmental triggers in the pathogenesis of the disease (**Table 3-6**).

Exposure to cow's milk (CM) in early neonatal life has received considerable attention. In the DiMe study, high consumption of CM protein was strongly associated with the emergence of beta cell autoantibodies and progression to clinical T1DM in initially unaffected siblings of children with T1DM.[151] In the Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes (FINDIA), infants were randomized to receive either CM formula, a whey-based hydrolyzed formula, or a whey-based formula free of bovine insulin, and those infants who received formula free of bovine insulin were significantly less likely to have autoantibodies at age 3 years than the infants who were fed CM.[152] More recently, the association between CM intake and beta cell autoimmunity has also been shown to be more marginal.[153]

Several mechanisms have been proposed to explain the link between CM proteins and beta cell autoimmunity. Bovine serum albumin is structurally very similar to islet protein p69, and a misdirected immune response against this protein may explain the immune-mediated beta cell injury.[154] In addition, infants fed CM-based formulas have significantly higher titers of antibodies to bovine insulin, and for that reason it has been theorized that early exposure to CM results in immunization to bovine insulin, a molecule that differs structurally from human insulin in only three amino acid positions.[155]

Early reports have suggested that children who were exclusively breast fed for prolonged periods as infants are at lower risk of developing T1DM.[156] The proposed mechanism of protection is decreased gut permeability and enterovirus infection protection.[157] This has not been confirmed in more recent studies that found no association of breast feeding or duration of breast feeding and emergence of beta cell autoantibodies.[158] For that reason the causal relationship still remains unclear. The ongoing Trial to Reduce IDDM in the Genetically at Risk (TRIGR) has randomized infants at increased risk of T1DM, at weaning, to receive either an extensively hydrolyzed formula or a conventional CM-based formula. Follow-up analysis is expected in 2014.

Gluten has also been incriminated as an important diabetogenic agent.[159] Two prospective studies have shown an association between introduction of cereals in infancy and early beta cell autoimmunity.[160,161] These studies found beta cell autoimmune susceptibility with introduction of

TABLE 3-6 Dietary Factors

DIETARY FACTOR	ROLE IN T1DM PATHOGENESIS	REFERENCES
Cow's milk	The DiMe study showed a strong association between consumption of cow's milk and T1DM.	151
Breast feeding	Early studies suggest that breast feeding for prolonged periods confers protection from developing T1DM.	156
Gluten	Gluten has been incriminated as an important diabetogenic agent, but the BABYDIET study showed no effect of gluten elimination on development of islet autoimmunity.	159, 164
Vitamin D	Finnish birth-cohort study showed that high-dose vitamin D supplements in infancy are associated with a decrease in risk of T1DM development.	165, 166
Omega-3 fatty acids	Higher intake was associated with lower risk of T1DM development.	169, 170

gluten in the first 3 months of life compared with introduction in the first 4 to 6 months.[160,161] The temporal association may be explained by immaturity of the gut and immune system in at-risk individuals.[162] Two small-scale studies showed that a gluten-free diet had no effect on beta cell autoimmunity but was associated with increased endogenous insulin secretion in family members at risk of T1DM.[159,163] More recently, a randomized clinical trial as part of the BABYDIET study, a primary prevention trial involving children with a first-degree relative with T1DM, showed no effect of gluten elimination on development of islet autoimmunity in genetically at-risk children.[164]

Vitamin D deficiency has also been implicated as a risk factor for T1DM.[165] Results reported by a Finnish study found that regular high-dose vitamin D supplements in infancy were associated with a decrease risk compared with no supplementation.[165] On the other hand, Finland, which is one of the areas in the world with the highest incidence of T1DM, reports an uptake of 80% for vitamin D supplements in children up to the age of 1 year.[166] There is also a striking difference in the annual incidence rate of T1DM in the neighboring populations of Finland and Russian Karelia (42/100,000 compared with 7.8/100,000), with no difference reported in the circulating vitamin D concentrations in pregnant women and schoolchildren.[167] Furthermore, Simpson and colleagues showed that neither vitamin D nor 25-hydroxyvitamin D (25[OH]D) levels were associated with risk of islet autoimmunity or T1DM in the DAISY population.[168]

Omega-3 fatty acids have also been reported to play a protective role in the development of T1DM. Studies have showed that higher omega-3 fatty acid intake is associated with lower risk of beta cell autoimmunity. In a case-cohort study based on the DAISY population, omega-3 fatty acid intake between the ages of 1 and 6 years was associated with lower risk of islet-autoimmunity.[169] A similar study from Norway supported these findings by showing that children with T1DM were less likely to have been given cod liver oil during infancy.[170]

Infectious Factors

Viruses, including herpesviruses,[171] mumps virus,[172] rubella virus,[173,174] retroviruses,[175] and in particular enteroviruses, have been implicated in the development of T1DM (**Table 3-7**). In animal models, viral infections can both promote and diminish autoimmunity. Viruses can initiate autoimmunity by at least four mechanisms (**Fig. 3-2**):

1. Molecular mimicry between viral proteins and autoantigens (e.g., PC2 protein of coxsackievirus mimics GAD65; rubella virus capsid protein mimics 52-kd islet protein; rotavirus mimics GAD and IA-2; cytomegalovirus mimics 38-kd islet protein; VP0 capsid protein in enterovirus mimics IAR/IA-2 tyrosine phosphatase)
2. Release of autoantigens following beta cell cytokine-induced injury, which are subsequently taken up by APCs and presented to T cells
3. Cytokine-induced upregulation of MHC and co-stimulatory molecules on APCs, enabling them to present self-peptides in immunogenic form to T cells
4. Interference with central and peripheral self-tolerance

Enteroviruses belong to the picornavirus family of RNA viruses. The proposed mechanism of how enterovirus contributes to the self-reactive process includes activation of interferon production, overexpression of class I HLA molecules, and chemokine-induced inflammation. Multiple studies have reported increased frequency of enteroviral RNA in patients with newly diagnosed T1DM.[176,177] Perinatal exposure to enterovirus may play a role in the pathogenesis of T1DM. Elfving and colleagues showed an increased prevalence of antienterovirus IgM in pregnant mothers whose children later developed T1DM during childhood; however, the known confounding effect of HLA-DR3/4 was not accounted for in their studies.[178–180]

The Australian BABYDIAB study followed approximately 500 babies with a first-degree relative with T1DM from birth, and found that rotavirus seroconversion was linked with the appearance of an increase in islet antibodies compared with HLA and age-matched controls.[181] These findings were not confirmed in prospective studies in Finland and Colorado.

Viral infections during childhood may also play a role in the development of immunoregulatory mechanisms that protect against diabetes.[182] The hygiene hypothesis proposes that improved hygiene in the Western World has led to a decline in immunity to common infections and increased incidence of autoimmunity. In other words, with early infectious exposures, young children build appropriate immune responses to pathogens. This idea is also supported by the findings that daycare attendance in early infancy confers protection against development of childhood diabetes.[183] The relationship between viral infection and autoimmunity appears to be temporal; studies have shown that enteroviral infections before weaning are beneficial and infections after are associated with susceptibility for T1DM development.[184–186] Vaccinations have not been associated with development of T1DM.[187,188]

In the last few years research has shed light on possible mechanistic pathways linking genetic predisposition to viral infections in the pathogenesis of T1DM. A good example is the *OAS1* gene, which encodes an antiviral enzyme that may induce beta cell damage through RNase L–mediated degradation of cellular RNA. Polymorphisms of *OAS1* produce an enzyme that is thought to result in a reduced apoptosis-mediated antiviral response, causing more extensive beta cell damage and initiation of autoimmune attack.[189] Another example is the *IFIH1* gene, which also encodes an RNA-activated apoptosis protein, and is associated with increased production of type 1 interferons that may contribute to the autoimmune attack of beta cells.[190,191] Polymorphisms of *IFIH1* confer both susceptibility and

TABLE 3-7 Viruses

VIRUSES	DESCRIPTION	REFERENCES
Enteroviruses	Multiple studies have reported increased frequency of enteroviral RNA in patients with newly diagnosed T1DM. In particular, coxsackievirus B4 is strongly associated with islet autoimmunity.	175, 176, 177
Rubella	Perinatal exposure may play a role in the pathogenesis of T1DM.	173, 174
Herpesviruses	These viruses are associated with autoimmune disease, occasionally with diabetes.	171
Mumps	Earlier reports indicate association with T1DM, but this remains controversial.	172
Rotavirus	Australian BABYDIAB study reports autoimmunity following rotavirus infection.	181

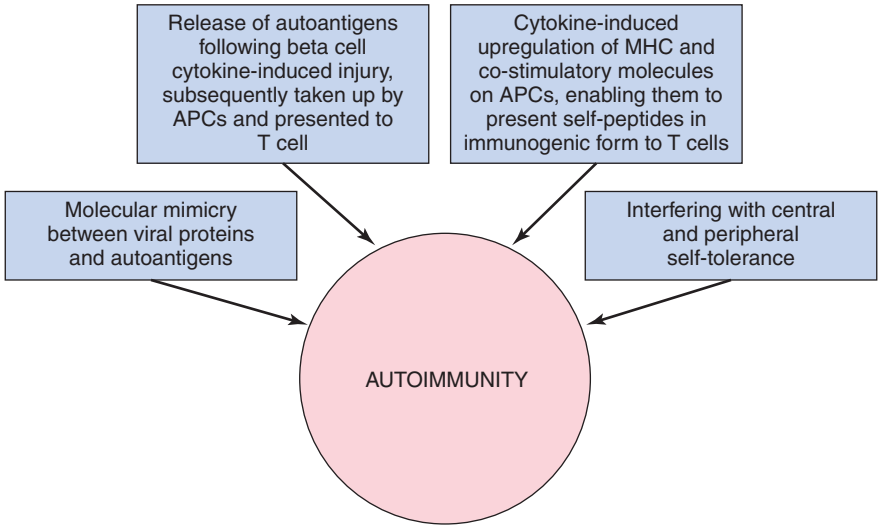


FIGURE 3-2 Viral-induced β cell autoimmunity. APC = Antigen presenting cells; MHC = major histocompatibility complex.

protection. IFIH1 alleles associated with higher IFIH1 levels are associated with an increased risk of developing T1DM, whereas protective IFIH1 alleles are linked with a decreased expression of *IFIH1*, and consequently a lower risk of T1DM.

Although the conclusion is controversial, studies have shown that susceptibility to the diabetogenic coxsackievirus B4 may be genetically predisposed, being restricted by HLA-DR and HLA-DQ alleles.[192] The HLA-DR3 allele has also been associated with enteroviral persistence in T1DM.[193] Whether HLA alleles provide a link between genetic susceptibility and viral triggers is still unclear and warrants further investigation.

Other Environmental Factors

Many other environmental factors have been proposed to be involved in the pathogenesis of T1DM. Increased weight gain in infancy has been reported to be an important risk factor,[174] but this has not been confirmed in larger studies. Children who develop T1DM have been shown to be both heavier and taller in infancy than their nondiabetic peers.[194]

Psychological stress may also constitute a trigger in the development of T1DM. Children with T1DM are, according to some studies, more exposed to stressful situations than controls.[195,196] The stress is especially frequent 2 years preceding diagnosis, and it may be the associated changes in hormonal and neuronal signals that contribute to the development of T1DM in genetically susceptible individuals.[197]

A potential protective factor is the microbiome, defined as the constellation of microorganisms that reside on the surface of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts, as shown in a study in NOD mice in which probiotic administration prevented T1DM.[198] In another study BB-DP rats were given *Lactobacillus* strains isolated from BB-DR rats and showed a reduced rate of diabetes development.[199]

SUMMARY

Significant advances have been recently made in our understanding of the etiopathogenesis of T1DM. We are also finally beginning to explore some possible mechanistic pathways linking genetic predisposition and exogenous triggers. Interruption of the disease process remains the long-term goal of T1DM research. Environmental modification likely offers the most powerful strategy for effective prevention. Most of our knowledge is derived from NOD mouse models. Although no animal model is able to fully describe the complexity of human T1DM, these models have allowed invaluable insight into the pathogenesis. Still, care is required in applying these findings to humans because many of them are unconfirmed, and for that reason there is a need for large prospective studies of high-risk children to gain further insight into environmental triggers in human T1DM and better understanding of infectious and genetic predispositions.

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4 The Metabolic Syndrome

Prevalence and Controversies in Clinical Context

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The metabolic syndrome (MetS) is defined as clustering of metabolic components that occur together more often than by chance alone and predispose to atherosclerotic vascular disease and diabetes. First descriptions of associated metabolic diseases occurred at the beginning of the last century when Kylin reported a connection between hyperglycemia, hypertension, and gout.[1] Thus, the intention with the introduction of MetS was primarily to get a clinical tool or common term for an interrelated cluster of metabolic diseases. Later, Vague realized the central role of android obesity in this cluster of diseases and connected MetS with atherosclerotic vascular disease.[2] This then was extended to "plurimetabolic syndrome," associated with increased risk of cardiovascular disease (CVD), by Crepaldi and colleagues.[3] In 1981 the first definition of MetS was published, connecting classical interrelated metabolic diseases with hypertension and atherosclerotic vascular diseases:

> *"The metabolic syndrome represents the common prevalence of obesity, hyper- and dys-lipoproteinaemia, maturity onset diabetes (type 2), gout and hypertension associated with increased incidence of atherosclerotic vascular disease, fatty liver and gallstones that develop on the basis of genetic susceptibility combined with overnutrition and physical inactivity. If this working hypothesis can be confirmed it provides the basis for integrated diagnostics and prevention of this cluster of diseases, which is of central importance for health care."*[4]

Despite these clear descriptions of the main components of MetS that might identify individuals at higher risk of atherosclerotic vascular disease that extend beyond classic risk factors—for example, age, sex, low-density lipoprotein (LDL) cholesterol, and smoking—the clinical and scientific usefulness of the concept of MetS is still an issue of debate. The main reason for this controversy might be the lack of a generally accepted definition of the syndrome: simple clinical measures are used to identify complex disorders, and cutoff limits were defined without sufficient epidemiologic data.

With the introduction of arbitrary cutoff limits for accepted components, there are now different definitions put forth by international and national institutions, including the World Health Organization (WHO),[5] the American Heart Association(AHA) and U.S. National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI),[6] and the International Diabetes Federation (IDF) (**Table 4-1**).[7]

The consequence of these different definitions based on arbitrary cutoff limits was a different estimation of the prevalence of patients with MetS.[8,9] Moreover, MetS according to IDF criteria had only a weak relationship to cardiovascular risk, because it was focused on insulin resistance, obesity, and dysglycemia as risk factors for diabetes. Thus it was not surprising that the usefulness of the concept was questioned in a joint statement of the ADA and the European Association for the Study of Diabetes (EASD).[10]

To overcome confusion and the waste of resources resulting from competing parallel investigations, a unifying concept and definitions were recently adopted (see **Table 4-1**).[11]

Here we analyze the association of MetS with CVD according to the primary idea behind a syndrome that is a tool to search for other components interrelated with the lead trait or disease.

ASSOCIATION BETWEEN METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE IN THE POPULATION

The global prevalence of MetS in the adult population varies from 15% to 50%. The estimated prevalence is affected by multiple factors such as age, sex, nutrition habits, lifestyle factors, socioeconomic conditions, and ethnicity as major determinants in addition to variability in the proposed definitions.[12,13]

MetS is not an absolute risk indicator because it does not involve many of the factors that determine absolute cardiovascular risk—for example, smoking, age, sex, and LDL cholesterol level.[11] Therefore it is not surprising that the usefulness of MetS as an independent cardiovascular risk indicator is a matter of controversy.

Most studies have revealed an increased risk for the development of CVD associated with MetS.[14–19] A meta-analysis of 36 longitudinal studies found a hazard ratio of 1.78 (95% confidence interval [CI] 1.58-2.00) for incident CVD events and death in individuals with MetS.[17] An analysis of the Framingham database also demonstrated an increased age-adjusted CVD risk of 2.88 (95% CI 1.99-4.16) for men and 2.25 (95% CI 1.31-3.88) for women with MetS.[18]

TABLE 4-1 Definitions of Metabolic Syndrome According to WHO, AHA/NHLBI, and IDF at the Beginning of the 21st Century and Consensus Statement 2009

WHO (1999)[5]	AHA/NHLBI (2005)[6]	IDF (2005)[7]	CONSENSUS STATEMENT CRITERIA (2009)[11]
NGT: Two criteria plus insulin resistance (highest quartiles of HOMA-IR) IFG or IGT: Two criteria	Three or more criteria	Central obesity as precondition Waist: Male ≥94 cm Female ≥80 cm Plus two or more criteria	
Dyslipidemia: TG ≥1.7 mmol/L (150 mg/dL) *and/or* HDL-C ↓: Male < 0.9 (35 mg/dL) Female <1.0 mmol/L (40 mg/dL) Hypertension: ≥140/90 mm Hg Obesity: BMI >30 kg/m^2 WHR: Male >0.9 Female >0.85 Microalbuminuria: ≥20 μg/min	Hypertriglyceridemia: TG ≥1.7 mmol/L (150 mg/dL) or Rx HDL-C ↓: Male <1.04 (40 mg/dL) Female <1.29 mmol/L (50 mg/dL) or Rx Hypertension: ≥130/85* mm Hg or Rx Central obesity: Male ≥102 cm Female ≥88 cm WC Fasting PG: ≥6.1 mmol/L (110 mg/dL) or Rx	Hypertriglyceridemia: TG ≥1.7 mmol/L (150 mg/dL) or Rx HDL-C ↓: Male <1.04 (40 mg/dL) Female <1.29 mmol/L (50 mg/dL) or Rx Elevated blood pressure: ≥130/85* mm Hg or Rx Fasting PG: ≥5.6 mmol/L (100 mg/dL) (OGTT recommended)	Hypertriglyceridemia: TG ≥1.7 mmol/L (150 mg/dL) HDL-C ↓: Male < 1.03 (40 mg/dL) Female: <1.29 mmol/L (50 mg/dL) Blood pressure: ≥130/85 mmHg Obesity/waist: depends on country-specific definitions Fasting PG: ≥5.6 mmol/L (100 mg/dL) or Rx

AHA = American Heart Association; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment, insulin resistance; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; NHLBI = National Heart, Lung, and Blood Institute; OGTT = oral glucose tolerance test; PG = plasma glucose; TG = triglycerides; WC = waist circumference; WHO = World Health Organization; WHR = waist-to-hip ratio.
*Systolic and/or diastolic.

Obviously there is an association between the increase of CVD risk and the number of features of MetS.[19] Recently published data from a large population-based meta-analysis that included more than 900,000 patients showed a twofold increase in cardiovascular events and a 1.5-fold increase in all-cause mortality rates in patients with MetS. The cardiovascular risk was still high in patients with MetS but without diabetes.[20] MetS according to National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) criteria could also be confirmed to be associated with CVD in Asian populations.[21,22]

There are few contradictory studies. In two large prospective studies, Sattar and colleagues[23] found that MetS had only a weak or no association with cardiovascular risk in an elderly population representative of the United Kingdom. In these prospective studies, however, MetS was a major risk factor for type 2 diabetes. Therefore the authors concluded that there is no common soil for diabetes and CVD based on MetS classification. Overall, there is sufficient evidence that patients with MetS are at twice the risk of developing CVD over the next 5 to 10 years,[11] and in all related studies there was an approximately twofold higher prevalence of MetS in comparable cohorts with major CVDs (coronary heart disease, cerebrovascular disease, stroke).[24,25]

It is interesting to see that in the United States, obesity, diabetes, and coronary heart disease develop in parallel, with some lag time for development of coronary heart disease (**Table 4-2**).[16]

The same phenomenon can be observed in the process of globalization and westernization in numerous other countries.[26]

The next question that arises is whether the outcome of CVD might be associated with MetS. In the Acute Coronary Syndrome (ACS) Israeli Survey, the outcomes of 1060 patients with ACS have been evaluated. Multivariable analysis identified MetS as a strong independent predictor of 30-day and 1-year mortality after ACS events, with hazard ratios of 2.54 (95% CI 1.22-5.31) and 1.96 (95% CI 1.18-3.24), respectively.[27]

In a study of 633 consecutive patients hospitalized with acute myocardial infarction, patients with (n = 290) and without (n = 343) MetS were compared. Acute myocardial infarction characteristics and left ventricular ejection fraction at admission were not statistically different between the groups. In-hospital case fatality was higher in patients with MetS compared with those without, as was the incidence of severe heart failure (Killip class II or greater). In multivariable analysis, MetS was a strong and independent predictor of severe heart failure, but not in-hospital death. Analysis of the predictive value of each of the five MetS components for severe heart failure showed that hyperglycemia was the major predictor (odds ratio [OR] 3.31; 95% CI 1.86-5.87).[28] These data demonstrate a worse outcome of CVD in patients with MetS.

There are fewer data available concerning MetS and cerebrovascular disease. A 14-year longitudinal cohort study comprising 1131 men (114 [10%] with and 1017 without MetS) has shown that MetS was associated with all types of stroke (OR 2.05 (95% CI, 1.03 to 4.11)); 65 strokes occurred during the monitoring, 47 of which were ischemic.[29]

After a 14-year follow-up in 2097 individuals with initial high prevalence of MetS (men 30.3%, women 24.7%), 75 men and 55 women sustained the first stroke. The age-adjusted relative risk of stroke in individuals with diabetes and MetS was high (OR 3.28; 95% CI 1.82-5.92), higher than that of any other MetS phenotype. In this study, with a high prevalence of MetS, MetS was also an independent risk factor for stroke in individuals without diabetes.[30]

ASSOCIATIONS BETWEEN METABOLIC SYNDROME AND INTERMEDIATE MARKERS OF CARDIOVASCULAR DISEASE

In a meta-analysis of data from patients with quantitative coronary angiography who underwent intravascular ultrasound, MetS was crudely associated with increased

TABLE 4-2 Prevalence of the Metabolic Syndrome According to Criteria of the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP-III); 1998 and 1999 World Health Organization Criteria, Diabetes (DM) and Coronary Heart Disease (CHD) by Age Group among U.S. Population ≥20 years

AGE	1998 WHO (N = 35.8 M)	1999 WHO (N = 41.3 M)	NCEP-ATP-III (N = 48.4 M)	DM (N = 14.0 M)	CHD (N = 12.2 M)
20-29 years (36 M)	4.9%	4.9%	6.0%	0.5%	1.9%
30-39 years (42 M)	11.0%	11.1%	14.2%	2.0%	3.4%
40-49 years (42 M)	19.3%	21.2%	24.6%	5.0%	4.5%
50-59 years (30 M)	28.5%	32.4%	36.5%	12.9%	7.5%
60-69 years (20 M)	35.3%	42.0%	48.1%	17.7%	11.9%
70-79 years (16 M)	35.0%	44.3%	48.4%	18.4%	16.1%
80+ years (9 M)	22.4%	27.7%	43.3%	15.5%	17.9%

Data from Alexander CM, Landsman PB, Teutsch SM, et al: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older, *Diabetes* 52:1210; 2003.

progression of plaque atheroma volume.[31] The main independent predictive factors for progression were hypertriglyceridemia (OR 1.26; 95% CI 1.06-1.49) and a body mass index exceeding 30 kg/m^2 (OR 1.18; 95% CI 1.00-1.40). However, after adjusting for these two components, MetS itself disappeared as an independent predictor for plaque atheroma progression. This is in line with studies from Sundström and colleagues,[32] who reported that MetS did not predict cardiovascular mortality independently of its individual components. This illustrates that the components of MetS have partially overlapping pathophysiologic mechanisms. Therefore their total combined effect could be less than the sum of individual effects.

In the Nijmegen Biomedical Study several noninvasive measurements of atherosclerosis were performed in 1517 participants aged 50 to 70 years with and without MetS.[33] Participants with MetS by NCEP-ATP III criteria were characterized by increased subclinical atherosclerosis compared with participants without any trait of MetS, as reflected by increased pulse wave velocity, increased carotid intima-media thickness (IMT), and thicker carotid plaques. The number of MetS traits was strongly associated with the severity of subclinical atherosclerosis. It is interesting to note that noninvasive measurements of atherosclerosis were already notably worse when one or two traits of MetS were present, with increasing prevalence and severity when four or five traits were present.

Carotid IMT and plaque volume were examined by ultrasound in a total of 166 individuals (73 with MetS versus 93 without MetS).[34] Increased IMT was observed in patients with versus without MetS (0.818 mm versus 0.746 mm; $P < 0.05$), as well as increased total plaque volume (125 ± 26 versus 77.3 ± 17.0 mm^3, respectively; $P = 0.039$).The higher the number of risk factors that characterize MetS, the greater the increase in the IMT.

In a cross-sectional study, MetS (n = 95) was associated with an increased common carotid IMT thickness of more than 16% ($P = 0.002$) and increased arterial stiffness of more than 32% ($P = 0.012$) compared with patients without MetS (n = 376).[35]

CARDIOVASCULAR DISEASES AND METABOLIC SYNDROME IN PATIENTS WITH ABNORMAL GLUCOSE TOLERANCE

It is a consistent finding that type 2 diabetes is present in more than 70% of patients with MetS.[36,37] In the Diabetes in Germany (DIG) study, a population-based observational study with more than 4000 patients, more than 75% had MetS by NCEP-ATP III criteria; most of them had three or four MetS component criteria (**Table 4-3**).[38] Among individual permuted phenotypes, the triplet of hypertension plus obesity and hypertriglyceridemia was the most commonly observed criterion identifying participants with MetS.

Already patients with impaired glucose tolerance (IGT) exhibit an increase in prevalence of MetS compared with subjects with normal glucose tolerance in the same age range. Approximately every second subject with IGT is diagnosed with MetS.[39,40]

Dysglycemia as a cardiovascular risk factor develops along a continuum up to the upper normal range for fasting and postprandial plasma glucose levels.[41,42] There exists overwhelming evidence that cardiovascular events and progression of vascular lesions in diabetes strongly depend on the presence of comorbidities such as hypertension and dyslipidemia—two major traits of MetS. As shown in **Table 4-3**, hypertension and hypertriglyceridemia are the most frequent single traits in type 2 diabetes patients in Germany.

With the dominance of hypertension and lipids as single risk factors, it is not surprising that different phenotypes or combinations of MetS bear different cardiovascular risks. In the DIG study the highest risk for all combinations that are displayed in **Table 4-4** was for those patients with three or more component criteria that included hypertension with any combination of two or more other traits. In all combinations with hypertension, women had a higher cardiovascular risk than men. However, quartets and quintets of component MetS criteria had no higher risk than triplets. This may be biased by small numbers of quartets and quintets. Overall, MetS was associated with an adjusted odds ratio of 1.38 (CI 1.04-1.82) for men and 1.67 (CI 1.08-2.59) for women.

TABLE 4-3 Prevalence of Metabolic Syndrome (NCEP-ATP III) and Its Traits in Type 2 Diabetes Patients: the Diabetes in Germany Study (DIG)

TRAITS	PREVALENCE (%)		
	Total	Male	Female
Obesity*	49.8	44.4	55.9
Hypertension	91.3	91.3	91.4
Hypertriglyceridemia	55.4	56.5	54.1
Low HDL-C	9.3	10.0	8.4
Only diabetes	2.4	2.6	2.2
Plus 1 trait	20.5	21.5	19.3
Plus 2 traits	35.3	36.4	34.1
Plus 3 traits	27.2	25.1	29.5
Plus 4 traits	4.0	4.2	3.8
Overall MetS	74.4	73.2	75.8

HDL-C = high-density lipoprotein cholesterol; HTG = hypertriglyceridemia; NCEP-ATP III = National Cholesterol Education Program—Adult Treatment Panel III.

*Difference by gender $P \leq 0.001$; χ^2 test. Obesity: body mass index exceeding 30 kg/m^2.

Data from Hanefeld M, Koehler C, Gallo S, et al: Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany (DIG) study, *Cardiovasc Diabetol* 6:13, 2007.

As demonstrated in **Figure 4-1**, hypertension in the DIG study is the most important single risk factor for cardiovascular disease in type 2 diabetes, with an odds ratio twice of that of MetS per se. This, however, is not an argument against the clinical usefulness of MetS as a construct in the setting of type 2 diabetes. In the DIG study, stepwise regression analysis to determine significance of MetS together with major established risk factors confirms overall MetS, age, male sex, LDL cholesterol levels, and smoking as independent risk factors.[38] The lesson from this and other studies is that a careful consideration of all traits of MetS in patients with type 2 diabetes is highly clinically relevant and can be used as guide for patient-centered treatment.

COMMON SOIL FOR METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE?

MetS has risen to increased clinical consideration and scrutiny together with the worldwide epidemic of obesity and diabetes. However, the pathophysiologic mechanisms leading to a cluster of metabolic diseases are not completely understood.[43] Although insulin resistance is the core abnormality of individuals with MetS,[44] there is insufficient evidence for a causal link between the two.[45]

A common hypothesis describes metabolic susceptibility as a central factor for the development of MetS (**Fig. 4-2**). This metabolic susceptibility is determined by polygenic variability of individuals[46] but also genetic defects of insulin signaling or dysfunctional adipose tissue and gene-environment interactions.[47,48] Once a sedentary lifestyle with decreased physical activity and high-calorie diet leads to the acquisition of body fat and development of overweight and obesity, a susceptible individual is at high risk to develop MetS.

Although several factors influence the development of MetS (see **Fig. 4-2**), abdominal obesity seems to be a prerequisite for its development,[49,50] and central obesity might causally link MetS with CVD.[47] Dysfunctional visceral adipose tissue is associated with increased secretion of inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and resistin and a decrease in the anti-inflammatory adipokine adiponectin.[51,52] Whether the inflammatory response of the visceral adipose tissue is primarily induced by intracellular fat accumulation or by infiltration of activated macrophages is still a matter of debate.[53]

Inflammatory cytokines are involved in the induction of endothelial dysfunction and insulin resistance.[47] Furthermore, the insulin-resistant state of obesity is characterized by increased plasma levels of free fatty acids that have cardiotoxic effects and impair the production of endothelial vasodilators.[54,55]

TABLE 4-4 Odds Ratios (95% Confidence Intervals) for Cardiovascular Disease of Different Phenotypes of Metabolic Syndrome in the Diabetes in German Study Population by Sex (NCEP-ATP III Criteria)

PHENOTYPE	TOTAL POPULATION	MALES	FEMALES
Triads			
DM + HBP + LHDL	5.67 (2.84-11.31)	4.25 (1.92-9.41)	10.90 (2.51-47.46)
DM + HBP + HTG	5.64 (2.29-13.87)	4.96 (1.80-13.71)	8.78 (1.21-63.91)
DM + HBP + Obes	6.17 (2.51-15.16)	6.11 (2.22-16.85)	9.19 (1.26-66.82)
DM + LHDL + HTG	1.14 (0.82-1.58)	0.85 (0.55-1.31)	1.78 (1.07-2.96)
DM + LHDL + Obes	0.90 (0.59-1.37)	0.54 (0.29-1.01)	1.76 (0.97-3.19)
DM + HTG + Obes	0.96 (0.79-1.17)	0.91 (0.71-1.17)	1.20 (0.86-1.68)
Quartets			
DM + HBP + LHDL + HTG	1.21 (0.87-1.69)	0.90 (0.58-1.39)	1.90 (1.13-3.20)
DM + HBP + LHDL + Obes	0.95 (0.62-1.46)	0.56 (0.30-1.04)	1.92 (1.05-3.50)
DM + HBP + HTG + Obes	1.01 (0.82-1.23)	0.93 (0.72-1.21)	1.29 (0.92-1.79)
DM + LHDL + HTG + Obes	0.86 (0.54-1.38)	0.47 (0.23-0.95)	1.85 (0.97-3.52)
Quintet			
DM + HBP + LHDL + HTG + Obes	0.92 (0.57-1.47)	0.49 (0.24-1.00)	2.03 (1.06-3.87)
Overall MetS	1.41 (1.12-1.78)	1.38 (1.04-1.82)	1.67 (1.08-2.59)

DM = diabetes mellitus; HBP = high blood pressure; HTG = hypertriglyceridemia; LHDL = low high-density lipoprotein cholesterol; NCEP-ATP III, National Cholesterol Education Program—Adult Treatment Panel III; Obes = obesity.

Data from Hanefeld M, Koehler C, Gallo S, et al: Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany (DIG) study, *Cardiovasc Diabetol* 6:13, 2007.

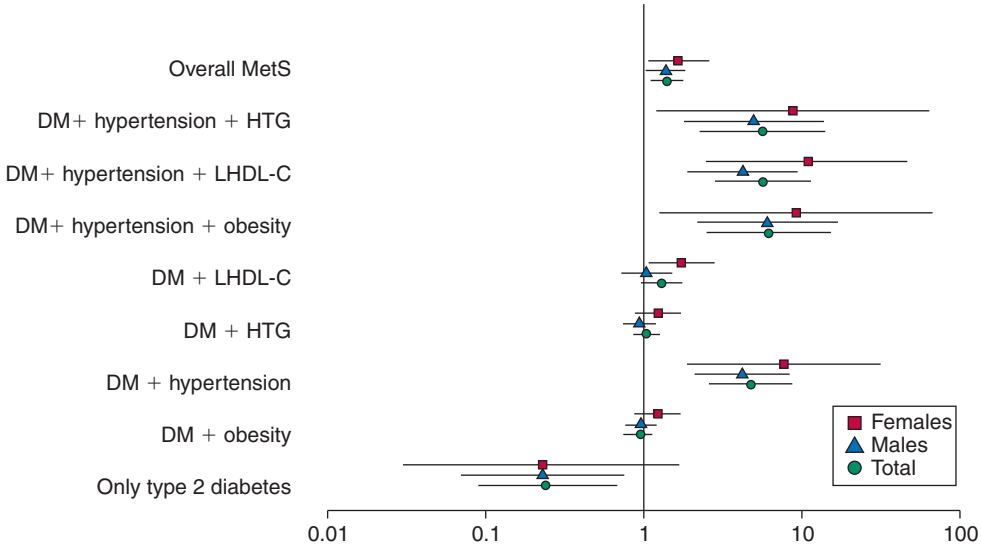


FIGURE 4-1 Odds ratios for major cardiovascular diseases by traits and phenotypes of the metabolic syndrome in patients with type 2 diabetes. *(Modified from from Hanefeld M, Koehler C, Gallo S, et al: Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany [DIG] study,* Cardiovasc Diabetol *6:13, 2007.)*

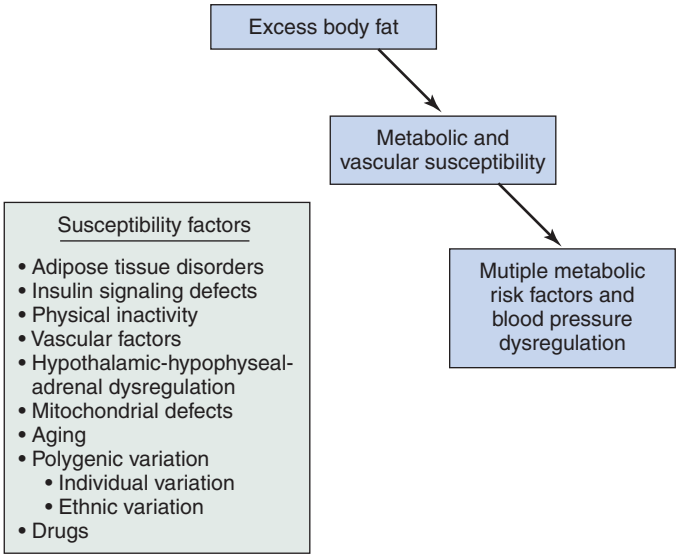


FIGURE 4-2 Pathogenesis of the metabolic-vascular syndrome. *(Modified from Cornier MA, Dabelea D, Hernandez TL, et al: The metabolic syndrome,* Endocr Rev *29:777, 2008.)*

Despite this complex pathophysiology as soil for MetS and associated diseases, we also have to keep in mind the strong impact of lifestyle and environment on the development of both MetS and cardiovascular disease. Therefore, if we consider a possible common soil for MetS and cardiovascular disease, we have to focus not on a one-dimensional genetic or pathophysiologic axis but on lifestyle changes accompanied by rapid behavioral and cultural transitions and mitigation of socioeconomic stress in the process of globalization and westernization.[26,56] As a prominent example, a close correlation between job stress and MetS was shown in the prospective Whitehall II population-based cohort study that was established in 1985 among 10,308 London-based civil servants who were 35 to 55 years of age at baseline.[57] Socioeconomic support and social status were assessed by questionnaires several times during 14 years of follow-up. The age-adjusted odds ratio for MetS after adjustment for grade of stress exposure in the highest grade was more than 2, versus low and moderate exposure.

A high social gradient for MetS that could not be explained by behavioral factors was reported from a subgroup analysis of the Copenhagen City Heart Study, a population-based cohort study that included 3462 women and 2576 men.[58,59] In general, lower-class people have higher risk for development of MetS and cardiovascular disease, as demonstrated during the transition period in Eastern bloc countries.[60]

Thus we find the common soil for MetS and cardiovascular diseases in times of globalization in a metabolic susceptibility as well as in an unhealthy lifestyle, in changes of socio-economic conditions, and in environmental factors.

METABOLIC SYNDROME AS GUIDE FOR PATIENT-CENTERED TREATMENT

As previously discussed, *metabolic syndrome* is a simple term for a heterogenic cluster of interrelated diseases with complex interaction with cardiovascular disease. However, there are core elements of a common soil, such as nutrition, physical activity, social behavior, and stress, as a basis for therapeutic lifestyle intervention. (See also Chapter 12.)

Beyond lifestyle, consideration for individualized drug treatment or interventional measures such as bariatric surgery targeting modification of each of the traits of MetS may be clinically prudent (see Chapter 6), and the presence or absence of prevalent cardiovascular conditions and their complications can be used as guide for a patient-centered yet integrated approach.

Lifestyle modification should always be the primary intervention to prevent the development of the components of MetS or to reduce the risk of CVD if MetS is already present. (See Chapter 12.)

A post hoc analysis of the prospective Diabetes Prevention Program (DPP) that included overweight people with both IGT and increased fasting glucose demonstrated a significant 41% reduction in the incidence of MetS after lifestyle modification compared with no intervention. Among those

participants without MetS at baseline, 53% of the placebo group but only 38% of the lifestyle group developed MetS during the follow-up period of 2.8 years.[61] A recent multicenter trial from Spain assessed the effects of a Mediterranean diet on the incidence of CVD in 7447 persons with cardiovascular risk factors; 61.4% met the criteria for MetS at baseline. After a median follow-up of 4.8 years, the hazard ratio (HR) for CVD events was 0.7 (95% CI 0.54-0.92) for the group assigned to a Mediterranean diet with extra-virgin olive oil compared with the control group. The greatest risk reduction was observed in people with components of MetS (e.g., hypertension, abdominal adiposity, dyslipidemia).[62]

Pharmacotherapy with glucose-lowering drugs can prevent the development of type 2 diabetes in people with IGT or increased fasting glucose (see Chapter 6). This has been demonstrated for metformin, acarbose, and thiazolidinediones.[63] In the DPP trial, metformin therapy reduced the incidence of type 2 diabetes by 31% and the incidence of MetS by 17%.[61,64] Comparable results regarding the prevention of type 2 diabetes was demonstrated with acarbose in the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM). People with IGT were assigned to treatment with either acarbose or placebo. After a mean follow-up of 3.3 years, the number needed to treat to prevent one case of newly diagnosed diabetes in patients with MetS was 5.8 versus 16.5 in those without MetS.[65] In addition, acarbose reduced the incidence of hypertension compared with placebo (HR 0.59 [95% CI 0.39-0.9]).[66] Thiazolidinediones have also been considered for use in people with MetS because they target a number of its components by improvement of glycemic control and insulin sensitivity; however, in contrast to metformin or acarbose, thiazolidinediones have been associated with adverse outcomes, especially congestive heart failure and weight gain, which have limited their use in clinical practice.

In a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which evaluated metabolic, cardiovascular, and renal outcomes in nondiabetic individuals with or without MetS who were assigned to initial hypertension treatment with a thiazide-like diuretic (chlorthalidone), a calcium channel blocker (amlodipine), or an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), treatment with chlorthalidone was associated with significantly higher risk for development of type 2 diabetes in the presence of MetS compared with the treatment with lisinopril.[67]

Thus consideration for use of specific glucose-lowering and blood pressure medications might be guided by the presence or absence of traits of MetS, because pleiotropic effects of such therapies may be used for an integrated approach to this cluster of interrelated conditions. However, no rigorous outcome data are available to place into clinical context such drug-induced progression to diabetes versus drug efficacy with regard to important clinical outcomes.

In addition to the metabolic abnormalities that determine the diagnostic criteria of MetS, there are clinical diseases and biochemical risk factors frequently associated with MetS (e.g., nonalcoholic fatty liver disease, sleep apnea, erectile dysfunction, albuminuria, hyperuricemia, increased biomarkers of low-grade inflammation; **Box 4-1**).[68–72] Some of these comorbidities might further increase the cardiovascular risk related to traits of MetS. Therefore, looking for comorbidities and their treatment should be an essential part of good clinical practice.

BOX 4-1 Diseases and Emerging Risk Factors Related to the Metabolic Syndrome

- Nonalcoholic fatty liver
- Sleep apnea
- Albuminuria
- Minor sexual, neural, and psychological abnormalities
- Social depression
- Increased subclinical inflammation
- Endothelial dysfunction
- Increased intima-media thickness
- Thrombophilia

In conclusion, currently available data support the evolving concept of MetS as the center of a complex network of cardiovascular risk factors that goes beyond the traditional CVD risk factors. The concept provides an integrated approach for screening, diagnostic testing, prevention, and treatment of diseases associated with MetS in the context of a patient-centered treatment strategy to prevent cardiovascular disease.

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5 Lifestyle Interventions for the Prevention of Type 2 Diabetes Mellitus

Peter E.H. Schwarz, Colin J. Greaves, Thomas Yates, and Melanie J. Davies

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In recent decades the world has experienced a significant increase in the number of patients with diabetes mellitus, primarily type 2 diabetes mellitus (T2DM).[1] Parallel to this, the increase is mostly attributable to a significantly higher frequency of diabetes diagnosis in the age group younger than 60, but also younger than 35 years of age. The growing economic burden in complex socioeconomic structures becomes obvious. The development of the diabetes epidemic is predicted to have a significant impact on global economic growth.[2] The situation requires fundamentally different approaches from national health care systems depending on national health care structures and their medical, environmental, social, and economic means. To respond rapidly in a coordinated fashion to the health threat of diabetes and its associated comorbidities, it is necessary to plan and prioritize high quality, standardized systems for diabetes prevention and care. This would ideally involve the development of a national diabetes program, with clearly defined goals, processes and responsibilities, which provides widely accessible diabetes prevention and care as part of the chronic care management system.

At the United Nations High-Level Meeting on Non-Communicable Diseases in September 2011 in New York, Ministers of Health requested international cooperation and policy decisions on diabetes according to the present context of globalization of health issues.[5] There was a consensus across countries that national programs for prevention and control of chronic diseases have to be developed and implemented and that strategies to monitor progress on implementation needed to be established. In April 2012 the European Diabetes Leadership Forum[6] was held, to discuss development of strategies on the political, medical, and patient-centered level for improving diabetes prevention, early detection, and management. Kofi Annan said at the meeting, "There is no other option than to act—we do not have enough money not to act."

THE GLOBAL EPIDEMIC OF TYPE 2 DIABETES: AN OVERVIEW

Currently, we are experiencing an epidemic growth in the number of people with diabetes worldwide.[1,7] An estimated 366 million people, corresponding to 8.3% of the world's adult population, have diabetes today, but the prevalence is expected to grow to 552 million by 2030, corresponding to 9.9% of the adult population (see also **Chapter 1**). This increase goes hand in hand with "westernization" of lifestyle, with consumption of more energy-dense food and decreasing physical activity. Driven by this development, diabetes affects more and more young people.

These changes have driven a huge increase in T2DM —the most common form of diabetes, particularly in young people, especially in their working age.[8] The medical burden is rising as patients with diabetes are developing a growing number of metabolic and cardiovascular comorbidities. The growing economic burden in complex socioeconomic structures becomes obvious. The continuation of the diabetes epidemic is predicted, and the World Economic Forum foresees the epidemic as a disaster likely to continue to worsen in the foreseeable future with a significant impact on global economic growth at least similar in scale to the recent banking crisis.[2]

The number of people affected by chronic diseases globally necessitates better chronic care management. The central programs, including early detection and treatment strategies as well as investment into the development and implementation of prevention programs,[4] focus on the prominence of lifestyle in the causal pathway of progression

to diabetes and represent an opportunity to use lifestyle promotion as a preventive strategy and key line of defense against the rising tide of T2DM.

EVIDENCE FOR SUSTAINABLE TYPE 2 DIABETES PREVENTION

There is now consistent evidence from randomized controlled trials (RCTs) across diverse countries and populations that lifestyle interventions, aimed at promoting physical activity, a healthy diet, and weight loss, can successfully reduce the risk of progression to T2DM by 30% to 60% in those with impaired glucose tolerance (IGT). IGT is an intermediate condition between normal glucose regulation and T2DM and is associated with a substantially elevated risk of progression to T2DM.[9] In 2001 the Finnish Diabetes Prevention Study (DPS) and in 2002 the U.S. Diabetes Prevention Program (DPP) as well as the Da Qing IGT and Diabetes Study[10] demonstrated that lifestyle modifications focused on losing weight, increasing physical activity, and improving diet could reduce the risk of progression to diabetes by almost 60%.[11] Similar findings were also seen in India,[12] Japan,[13] and China.[10] There was a strong dose-response effect for people who adopted four or five lifestyle changes; the progression rate after 7 years was reduced by 80% compared with those making no changes (**Fig. 5-1**).[14] There is consistent evidence that some pharmaceutical agents, such as metformin—a drug that is effective for glucose lowering in people with T2DM—can prevent the onset of diabetes in high-risk populations by 31% in people with IGT,[12,15] and other agents have also been proven to be effective,[16,17] but the evidence consistently suggests that lifestyle interventions are more effective than pharmacologic interventions in preventing the onset of T2DM.[18]

Economic evaluation has demonstrated the cost-effectiveness of primary prevention of T2DM.[19] However, despite the evidence, it remains questionable whether these programs are feasible at a population level. The challenge, therefore, is to establish a scientifically based structural framework for efficiently managing nationwide prevention programs.

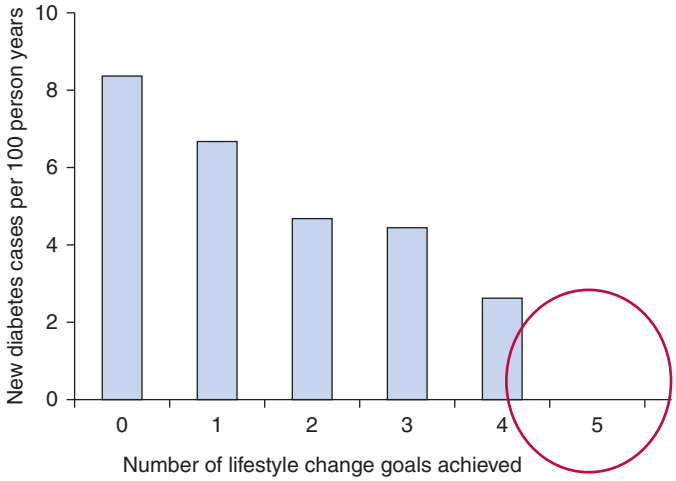


FIGURE 5-1 Dose-response effects of lifestyle behavior change (from 0 to 3 years) on diabetes incidence (at a median 7 years) in people with impaired glucose regulation (based on data from the DPS[1]). The program goals were (1) no more than 30% of daily energy from fat, (2) no more than 10% of energy from saturated fat, (3) at least 15 g of fiber per 1000 kcal, (4) at least 30 minutes of moderate physical activity per day, and (4) at least 5% weight reduction.

Currently the evidence regarding short-term reduction of diabetes risk and conversion to T2DM in people with IGT is very good, but the major question remains how sustainable this effect may be. A recent report has summarized the long-term effect of T2DM prevention, pointing out a significant sustainability of the effect if the initial intervention was able to achieve lifestyle change.[20] The first study suggesting a sustainable effect was the Malmö Feasibility Study.[21] This study tested the effect of exercise and diet on incidence of T2DM among 161 men with IGT. After a 5-year study period, 11% of the men in the intervention group had developed T2DM compared with 29% of the men in the reference group who did not want to join in lifestyle intervention. After the 12 years of follow-up, all-cause mortality was significantly lower in the former intervention group (6.5/1000 versus 14.0/1000 person-years, $P=0.009$) and was similar to that in healthy individuals without any glucose disturbance.[22]

The Da Qing study[10] undertaken in China included 577 men and women with IGT who were randomized into an intervention and a control group. The interventions included diet alone, exercise alone, and a combination of diet and exercise. The lifestyle intervention was for a period of 6 years and resulted in lower cumulative T2DM incidences in all three intervention groups (41% to 46%) compared with the control group (68%). It is interesting to note that the participants in the study were relatively lean, so that the weight reduction was relatively small. In the participating clinics assigned to the dietary intervention, the recommendation included a high-carbohydrate (55% to 65% caloric intake) and moderate-fat (25% to 30% caloric intake) diet. This study indicated that it is not body weight reduction alone that is important for the prevention of T2DM. Also, other lifestyle issues are important, and body weight may be a summary indicator for several dietary and activity factors.[10] The 20-year follow-up of the study showed a sustained 43% reduction in the incidence of T2DM in the intervention group compared with the control participants.[20] It is surprising to note that there was no significant effect in the reduction of cardiovascular disease or mortality, but a sustained effect in reducing the prevalence of microvascular disease in diabetes patients.[23] The Da Qing study is the study with the longest follow-up. In essence, the study shows that lifestyle intervention enables a significant delay in the conversion to T2DM in those at risk and, for a period of at least 20 years, significantly prevents T2DM. For persons who develop T2DM, the intervention significantly reduces the development of microvascular complications.[10,23]

The DPS was a multicentered trial carried out from 1993 to 2001 in Finland in five clinics.[24] The main objective of the study was to test the effect of 3 years of lifestyle intervention on the incidence of T2DM compared with a control group; 522 men and women were recruited into the study and randomly allocated into a control and an intervention group. The reduction in incidence of T2DM was 58% associated with an average weight reduction of 4.5 kg in the intervention group versus 1.0 kg in the control group ($P<0.001$) after 1 year, and similar results were maintained after 3 years. Overall, visceral obesity, dietary habits, and exercise habits improved significantly and were independently associated with T2DM risk reduction.[25,26] The cumulative incidence of T2DM was 11% (95% confidence interval [CI] 6%-15%) in the intervention group and 23% (95% CI 17%-29%) in the control group after 4 years, and thus the risk of T2DM

was reduced by 58% ($P<0.001$) in the intervention group compared with the control group.[27] Subsequent analyses using data collected during the extended follow-up of the study showed that after a follow-up time of 7 years, a marked reduction in the cumulative incidence of T2DM was sustained, reaching a risk reduction of 43%.[14] The corresponding incidence rates were 4.6/100 and 7.2/100 person-years between the intervention and control groups. The 10-year follow-up results of the effect of the lifestyle intervention in the T2DM prevention study included total mortality and cardiovascular risk and showed a significant reduction in total mortality but, similar to the findings of the Da Qing study, no effect on reducing cardiovascular morbidity. It is interesting to note that when the DPS intervention and control groups together were compared with a population-based cohort including people with IGT, adjusted hazard ratios were 0.21 (95% CI 0.09-0.52) and 0.39 (95% CI 0.20-0.79) for total mortality and 0.89 (95% CI 0.62-1.27) and 0.87 (95% CI 0.60-1.27) for cardiovascular morbidity. Thus the risk of death among the DPS participants was markedly lower than in a population-based IGT cohort.[20]

The DPP was a U.S. multicenter randomized clinical trial.[28] It compared the efficacy and safety of three interventions—an intensive lifestyle intervention, standard lifestyle recommendations combined with metformin, and placebo.[20] The goals of the dietary intervention were to achieve and maintain a 7% weight reduction through consumption of a healthy low-calorie, low-fat diet and to engage in physical activities of moderate intensity (such as brisk walking) for 150 min/wk or more. The intensive lifestyle intervention reduced T2DM risk after a 2.8-year mean follow-up by 58% compared with the placebo control group. Lifestyle intervention was also shown to be superior to metformin treatment, which resulted in a 31% risk reduction for incident T2DM compared with placebo. At the 1-year visit, the mean weight loss was 7 kg (approximately 7%).[20] After the publication of the main results in 2002, the randomized trial was stopped and the participants were invited to join the Diabetes Prevention Program Outcomes Study (DPPOS).[29] During the follow-up, all participants, regardless of their original treatment group, were offered lifestyle counseling. During the overall follow-up of 10 years (calculating from the randomization to the DPP), T2DM incidence in the original lifestyle intervention group was reduced by 34% compared with the control group. However, during the postintervention follow-up, T2DM incidence was not statistically different between the treatment groups (5.9/100 person-years in the former intervention group and 5.6/100 in the placebo control group), confirming that lifestyle intervention that was initiated in the former placebo control group was successful even after several years of follow-up without any active intervention.[20]

THE ELEMENTS OF TYPE 2 DIABETES PREVENTION

Identifying People at Risk

The question of who should be targeted for diabetes risk reduction is not easy to answer because the effect of an intervention program to prevent T2DM in adulthood depends on the setting where the intervention is performed, the effectiveness of the intervention in addressing the high-risk individual, accessibility and affordability, and a variety of additional variables.[18] However, the main considerations when deciding who should be targeted for T2DM prevention are the effectiveness and affordability of the interventions available after the high-risk person has been identified. Screening for diabetes risk makes no sense without availability of a successful and sustainable intervention program.[4] Interventions can have various approaches, strategies, and concepts. Furthermore, strategies for targeting people at high risk will vary significantly among different settings and different population groups. The risk factors for T2DM are well recognized, and T2DM is often preceded by a period of IGT that is characterized by increasing insulin resistance and beta cell dysfunction.[30] Visceral obesity plays a key role in triggering the development of insulin resistance and increasing T2DM risk.[18] It is also recognized that many people with T2DM remain undiagnosed and that patients with long diagnostic delays often have significant complications at diagnosis.[31] This suggests that combined screening for both IGT and undiagnosed prevalent T2DM could be a pragmatic option. Indeed, data show that screening for both conditions together is cost-effective, particularly when lifestyle and pharmacologic interventions are then used to delay the onset of T2DM in high-risk individuals.[32] Screening for T2DM and IGT in high-risk populations is now recommended by a number of international diabetes associations [33–35]; a plethora of tools are available to identify people at increased risk of T2DM, and there is little evidence of long-term, physical or psychological harm from such screening.[36]

The consensus (based on screening approaches used in practice in the United States, Germany, Australia, Finland, the United Kingdom, and other countries)[4,37–39] seems to favor a targeted, staged approach with the first step being to identify those at high risk and a second step being to confirm glycemic status (whether T2DM, IGT, or normoglycemia).[40] Preliminary data about this broad approach suggest that it is more cost-effective to use a noninvasive screening tool as the first stage in screening rather than a blood test.[41] Risk scores tend to be based around risk factors such as age, gender, body mass index (BMI), ethnicity, family history of diabetes, and the use of antihypertensive medication. Risk scores have been shown to have good sensitivity and specificity for identifying diabetes risk.[40] For example the Finnish Diabetes Risk Score (FINDRISC), the Danish Risk Questionnaire, the Cambridge Risk Score, the Leicester Diabetes Risk Score, and the Indian Score have all been associated with a sensitivity of 76% to 77% and specificity of 55% to 72%, with a positive predictive value varying from 7% to 11%.[40] The most common approach used is the FINDRISC questionnaire, which individuals use to self-assess their risk based on seven questions; FINDRISC has been shown to have good validity at predicting future diabetes over a 10-year period.[42] It is important to note that although FINDRISC has been validated for use in various countries,[43] given the varying profile and prevalence of risk factors in different settings,[30] the score performance cannot be generalized from one country to another. It is therefore important that risk scores be validated in the population in which they will be applied. The other approach is to use data that are routinely available to the general practitioner (e.g., the Cambridge Risk Score, the QDScore, the Leicester Practice Risk Score).[40]

The second stage involves diagnostic testing. In practice, this usually consists of either a fasting glucose or a hemoglobin A1c (HbA1c) test, although oral glucose tolerance

testing can also be used. A recent statement by the International Expert Committee of the World Health Organization (WHO) has advocated that an HbA1c of 6.5% (48 mmol/mol) or higher can now be used to define T2DM.[44] However, there is no clear consensus on how or whether HbA1c should be used to classify diabetes risk below this level.[45] The American Diabetes Association (ADA) tentatively suggested that an HbA1c value of 5.7% to 6.4% indicates a high risk of T2DM, whereas an international expert committee suggested a range of 6.0% to 6.4%.[34,46] The latter range was also recently endorsed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, which now recommends that HbA1c be used to identify those with a high risk of T2DM and that patients with a value of 6.0% to 6.4% be referred to a T2DM prevention program.[33] Prospective data from the United Kingdom support the use of 6.0% to 6.4% to define an at- risk category, because individuals in this group were found to have a risk of future T2DM that was twice that in individuals with a value of 5.5% to 5.9%.[18] However, other data from Germany suggest that an HbA1c threshold of 5.7% is likely to have the best sensitivity and specificity for detection of future T2DM risk[45] but demonstrate that the combination of HbA1c and the 1-hour plasma glucose concentration after a 75-g oral glucose load in predicting future T2DM risk was significantly better in a multivariable model than either one of them alone. The 1-hour plasma glucose concentration has previously been shown to be a strong predictor of T2DM risk[47] and also other chronic disease[48] but has major logistical issues. Furthermore, the optimal HbA1c cut point for identifying individuals at increased diabetes risk is 5.7%[45] and not 6.0% as originally suggested by the ADA Expert Committee.[46] If HbA1c exceeding 6.0% had been used to identify individuals at increased risk for future T2DM, only about one third of patients who developed T2DM would have been identified. Thus, use of an HbA1c cut point of 5.7% together with the 1-hour plasma glucose concentration[45] would identify many additional high-risk individuals who could benefit from an intervention program.[45]

The most cost-efficient way to balance resources against risk has yet to be determined. In the meantime, the balance that is struck may depend to a large extent on pragmatic considerations, particularly financial constraints.[38] It is acknowledged that, along with strategies for identification and intervention for those with a high risk of a widely prevalent condition such as T2DM, it is also fundamentally important to use initiatives that are aimed at shifting the distribution of known risk factors, such as BMI in adults or BMI percentiles in childhood and waist circumference within the population as a whole.[49] Strategies for primary prevention on a public health level and high-risk strategies need to work in parallel.[39]

Physical Activity

Epidemiologic, experimental, and randomized controlled clinical study trial-level evidence has consistently demonstrated that levels of physical activity are centrally involved in the regulation of glucose homeostasis, independent of other factors including adiposity.[50,51] A modest increase in walking activity, toward levels that are consistent with the minimum recommendations, significantly improved 2-hour postload glucose levels by 23 mg/dL over 12 months in high-risk overweight and obese individuals despite the absence of any significant change in body weight or waist circumference.[52] This may correspond to a greater than 60% reduction in risk of developing T2DM within 24 months.[53] These findings were consistent with findings from other studies,[26] but replication of the results is needed and attempts are under way. Although the promotion of physical activity is a cornerstone of effective T2DM prevention programs, the role of physical inactivity in helping identify T2DM risk is less clear and more problematic for several reasons. First, physical inactivity is highly prevalent among the general population; it has consistently been shown that 50% to 80% of the population in both developed and developing countries fails to meet the minimum recommendations for health.[54] Indeed, when physical activity levels are objectively measured, rather than by subjective self-report, around 95% of the population fail to meet the minimum requirements for health, making inactivity a near universal condition.[54] Therefore commonly used definitions of physical inactivity do not provide a clear mechanism for stratifying diabetes risk. Second, methods that rely on self-reporting by individuals of their activity levels are highly inaccurate and unreliable. For example, an internationally used and validated self-reported measure of physical activity described as little as 10% of the variation in objectively measured levels through accelerometry[55]; in contrast, simple measures of adiposity, such as BMI and waist circumference, are reasonably accurate on a population level. For these reasons, self-recording levels of physical (in)activity has not been shown to add to the predictive power of diabetes risk scores or to be useful when incorporated into other methods of quantifying diabetes risk. However, it is important that physical inactivity, as with other lifestyle variables, be considered for the individual assessments of T2DM risk.[18]

To be successful, lifestyle intervention programs should focus on types of physical activity that are acceptable to most of the population. Walking has consistently been shown to be the most popular choice of physical activity, including in those with a high risk of T2DM.[26] Indeed, walking for 150 min/wk during leisure time is associated with a 60% reduction in the relative risk of T2DM compared with those that did little or no walking in their leisure time.[26] Of importance, walking is associated with fewer barriers than other forms of physical activity in black and minority ethnic populations dwelling in developed countries, such as South Asians.[56]

Wearing a pedometer and keeping a daily step log have been widely advocated as effective self-regulatory strategies in the promotion of increased ambulatory activity, and their use has consistently been shown to successfully promote increased physical activity.[57] The success of pedometer interventions is centered on the pedometer's ability to raise awareness of current activity levels, provide objective feedback to the individual, and facilitate clear and simple goal setting. To be effective, it is essential that realistic and personalized step-per-day goals be used; goals that are too ambitious can often be demotivating and lead to failure. Sedentary individuals (fewer than 5000 steps/day) should initially aim for an average increase in ambulatory activity of around 2000 steps/day conducted at a moderate to vigorous intensity, which is roughly equivalent to an additional 150 minutes of walking activity per week.[58] Alternatively, the categories of ambulatory activity shown in **Table 5-1** can be used to guide lifestyle interventions. For example, those in the sedentary or inactive categories could initially

TABLE 5-1 Physical Activity Categories Based on Steps per Day

CATEGORY	STEPS PER DAY
Sedentary	<5,000
Low (typical of daily activity excluding volitional activity)	5,000-7,499
Moderate (likely to incorporate the equivalent of around 30 minutes of moderate-intensity physical activity per day)	7,500-9,999
High (likely to incorporate the equivalent of around 45 minutes of moderate-intensity physical activity)	10,000-12,499
Very high (likely to incorporate the equivalent of over 45 minutes of moderate-intensity physical activity)	>12,500

Data from Tudor-Locke and Bassett, 2004.[58]

aim to increase their ambulatory activity by at least 2000 steps/day. Those in the moderate category could be encouraged to try and enter the high category, and those achieving the high or very high categories should be helped to at least maintain their activity levels. For people who have significant barriers to walking, such as joint problems, alternative forms of physical activity, such as cycling, water aerobics, or swimming, should be encouraged.

Nutritional Aspects

Obesity is one of the most important risk factors for T2DM, and population trends in obesity and T2DM run in parallel.[59] The pathophysiology of adiposity with regard to the development of T2DM is not fully understood; however, several mechanisms that may interact have been identified. Adipose tissue, especially the tissue surrounding internal organs (visceral fat), is today regarded as an active endocrine organ that secretes a variety of proinflammatory adipokines that act at both the local and the systemic levels.[60] Cornier and colleagues have reported that increasing adipose tissue mass leads to changes in the secretion of these adipokines as well as increased turnover of free fatty acids, which bring on insulin resistance, the harbinger of metabolic disturbances leading to T2DM.[61]

Even though the basic cause of excess body fat accumulation is an imbalance between energy intake (i.e., dietary intake) and expenditure, the factors predisposing to the development of overweight and obesity are multifactorial and poorly understood. Nevertheless, regular physical activity, high dietary intake of fiber, and reduced intake of energy-dense micronutrient-poor foods were identified by WHO as lifestyle targets for reducing obesity.[62] In the DPS, the dietary energy density was found to be associated with achieved weight reduction,[14] which supports the intuitive recommendation to increase foods with low energy density such as vegetables and fruits to increase satiety while reducing total energy intake. An increased understanding of these mechanisms will be helpful in providing prioritization of behavioral targets for future prevention programs.

Nutritional Recommendations

For most people, weight reduction is difficult to sustain. Fortunately, T2DM prevention studies have shown that changing one's lifestyle is effective without significant weight reduction.[10,12,52] An important contributor is physical activity; however, the composition of diet seems to be important as well. Epidemiologic studies have suggested that several dietary factors may either increase diabetes risk (e.g., intake of refined grains, red and processed meat, and sugar-sweetened beverages; heavy alcohol consumption) or decrease it (e.g., intake of whole-grain cereal, vegetables, legumes, nuts, dairy, and coffee; moderate alcohol consumption), independently of body weight change.[18] The suggested mechanisms behind these observations include improvement of insulin secretion and/or insulin resistance as a result of reduced glycemia and lipidemia, reduced ectopic fat, reduced low-grade inflammation, changes in cell membrane phospholipids, and improvement of intestinal peptide secretion.[18]

In addition to weight reduction and increased physical activity, the Finnish DPS aimed at reduced total and saturated fat intake and increased fiber density of the diet.[63] The post hoc analyses showed that T2DM risk reduction was clearly associated with the achievement of these lifestyle goals. In the U.S. DPP study, dietary goals were reduced energy intake (to achieve weight reduction) and reduced total fat.[28] The T2DM prevention studies from China, India, and Japan aimed at reduced fat, energy, alcohol, and refined carbohydrates and increased fiber.[10,12,13] A recent study from Spain showed that adoption of a Mediterranean diet, characterized by a high intake of vegetables, fruits, legumes, extra virgin olive oil, nuts, fish, whole grains, and red wine, also decreases T2DM incidence remarkably,[64] without body weight reduction.

A pragmatic way to prevent T2DM therefore would be to focus on diet composition and physical activity. A strict diet emphasizing dietary restriction and avoidance of certain food groups (e.g., sources of fat or carbohydrates) and aiming solely at weight reduction may be more efficient for achieving weight loss in the short term, but may not be sustainable in the long run.[65] Diet may well vary according to food culture, food availability, and personal preferences and yet follow the same general principles:

- High intake of vegetables and fruits should be encouraged.
- Grain products should mainly be unrefined, with high natural fiber content.
- Vegetable sources of fat with low saturated fat content (such as olive oil) should be preferred.
- As a source of protein, nuts, legumes, dairy products, and fish should be favored and red meat limited.
- The intake of highly processed foods (e.g., processed meat, sweetened beverages, confectionery) should be limited.

The Right Intervention for the Person at Risk

Supporting Behavior Change

As described earlier, there seem to be several possible routes to nonpharmacologic diabetes prevention, but a common factor is the need to support sustained changes in lifestyle behaviors. However, achieving the required changes reliably is challenging. Both clinical intervention programs[66] and "real-world" diabetes prevention programs demonstrate wide variation in their ability to deliver weight loss or changes in physical activity.[18] It is therefore of importance to be able to characterize the components of lifestyle interventions that are reliably associated with increased effectiveness (**Fig. 5-2**). Only by understanding what makes interventions effective can we design diabetes prevention programs that will deliver the expected benefits and optimize cost-effectiveness in scalable, real world prevention programs.

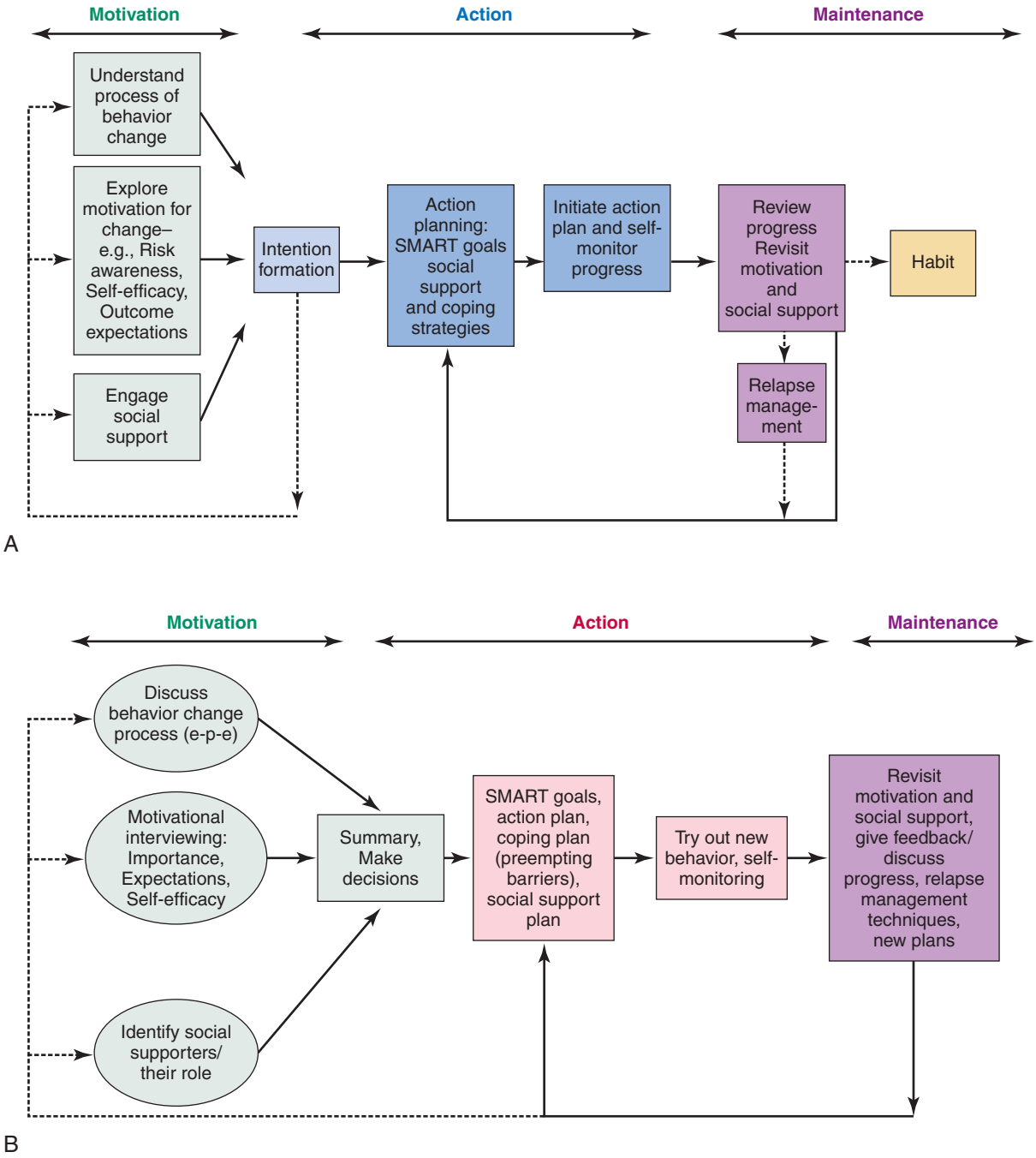


FIGURE 5-2 Behavior change model and behavior change techniques based on SMART goals: *S*pecific, *M*easurable, *A*chievable, *R*elevant, *T*ime related.[66] e-p-e = elicit-provide-elicit (a technique for patient-centered information exchange).

A recent analysis of reviews systematically examined a wide range of evidence from existing high-quality reviews of RCTs of interventions to support changes in diet and/or physical activity in people at high risk of developing T2DM.[67] Based on the grading of 129 analyses that related intervention characteristics to effectiveness, evidence-based recommendations were developed. These recommendations are broadly consistent with other recent international guidelines for supporting lifestyle change in people with high cardiovascular risk with T2DM[68] and obesity.[69]

Applying these recommendations may help to guide the selection of intervention components in a way that maximizes the likely effectiveness of diabetes prevention programs. However, it is worth noting that the evidence base on the best strategies for supporting behavior change is far from complete. Individuals with high T2DM risk from different backgrounds and cultures may be responsive to a number of different strategies that modify the cognitive, social, and emotional processes that underpin their lifestyle behaviors. There are also a number of possible modes of intervention beyond persuasive face-to-face interaction, including modification of the physical environment and changes in food pricing or regulation and taxation. Hence, there may be considerable opportunities to further increase the efficiency and cost-effectiveness of programs to support lifestyle behavior change (see also **Chapter 12**).

Considerable attention is also needed to address the issue of maintenance of lifestyle changes. Long-term follow-up of

weight loss interventions shows a clear pattern of weight regain over 5 to 10 years, even in the successful diabetes prevention research studies.[29,65] It is likely that when weight loss is achieved through changes in diet or physical activity that are challenging for people to adhere to or that they do not enjoy, these changes will not be sustainable in the long term. Recent data from a meta-analysis of multiple long-term cohort studies indicate that a habitual energy imbalance of an excess of only 50 to 100 kcal/day seems sufficient to cause the gradual weight gain observed in most adults. Consequently, "modest, sustained changes in lifestyle could mitigate or reverse such an energy imbalance." Hence, promoting a series of small changes that people can easily live with, rather than dramatic changes in diet or activity, may be a strategy worth further investigation.

RECOMMENDATIONS FOR TYPE 2 DIABETES PREVENTION PRACTICE

The European Union supported the IMAGE project (Development and Implementation of a European Guideline and Training Standards for Diabetes Prevention), a multiprofessional initiative to develop practice recommendations for diabetes prevention practice.[18] More than 100 experts in this field worked for 2.5 years to prepare an evidence-based guideline for T2DM prevention,[37] a toolkit for diabetes prevention practice,[38] a guideline for evaluation and quality management in T2DM prevention,[70] and a European training curriculum for prevention managers.[71]

The major output of the IMAGE project—relevant for prevention practice—is the practical diabetes prevention guideline called "Toolkit for the Prevention of Type 2 Diabetes." This toolkit is developed for all professionals involved in diabetes prevention: those working in primary health care services, physicians, physical activity experts, dietitians, nurses, and teachers, but also stakeholders and politicians. The Toolkit condenses the essence of what is necessary to build up the management of a diabetes prevention program, with financial, intervention-related, and quality assurance aspects, and refers to the latest evidence in diabetes prevention. The core of the Toolkit describes elements of an effective lifestyle intervention program and gives the core goals of lifestyles (behavior, physical activity, and diet) and finishes with an overview of how to evaluate intervention programs and how to establish quality assurance. It provides several recommendations that may help in planning and implementing T2DM prevention programs worldwide.[4,20,72]

The Toolkit provides a good balance between clear, accurate information and practical guidance; it is not, however, intended to be a comprehensive source of information. Specifically, detailed instructions about how to achieve and maintain weight reduction, which is one of the main issues in T2DM prevention, are not given because local and national guidelines as well as other sources of information are available elsewhere. Furthermore, intervention delivery staff members are assumed to have basic knowledge about, for example, diet and physical activity and their health effects and about supporting behavior change. Finally, the Toolkit is not designed to be used to provide intervention materials to be delivered directly to those participating in prevention interventions, although it does contain some examples of information sheets and materials that might be used with participants.

Contents of the Type 2 Diabetes Prevention Toolkit

The Toolkit starts with an executive summary including the rationale for T2DM prevention.[38] It is followed by a chapter representing the background (T2DM prevalence, risk factors, consequences, evidence of successful prevention) and giving instructions about the planning and development of prevention programs and the identification and recruitment of participants at high risk for T2DM. One of the core items of the Toolkit is the description of what to do and how to do it. Behavior change is a process that requires individual attention and effective communication to achieve motivation, self-monitoring, sustained support, and other intervention to prevent and manage relapses (see **Fig. 5-2**). This section includes a model of intervention including empowerment and patient-centered messages. It is followed by key messages on behaviors (physical activity and diet) that are important in prevention of T2DM (**Tables 5-2** and **5-3** and **Box 5-1**), and practical advice for patient-centered counseling. The focus is on long-term, sustainable lifestyle changes.

A brief guide for evaluation and quality assurance in reference to the quality and outcome indicators is included. This section is followed by a consideration of possible risks and adverse effects. The IMAGE Toolkit main text ends with a positive mission statement, emphasizing what can be achieved if we work together. The appendices give the reader a set of easy-to-use tools including a checklist for prevention program development, templates for goal setting and for food and physical activity diaries, an example of a risk-screening questionnaire (the FINDRISC questionnaire), and a template for evaluation and quality assurance data collection.[38]

Intervention Cost and Scarce Resources

There is clearly tension between the evidence-based recommendation for maximizing intervention intensity (number or frequency of contacts) and the practical availability of resources (suitably trained staff and funding) for diabetes prevention. However, this tension might be reduced in several ways. These include the following:

- *Using group-based interventions.* There are several good examples of group-based interventions that produce levels of weight loss similar to those in the large diabetes prevention studies, at least in the short term.[73,74] Group-based intervention also costs less than individual intervention.
- *Reducing staff costs.* Lifestyle interventions can be delivered successfully by a range of staff, including physicians, nurses, dietitians and nutritionists, exercise specialists, and nonprofessionals.[67] More research is needed to define the range of personal skills and type of training required to maintain program effectiveness.[71]
- *Applying self-delivered and Internet-based approaches.* This type of intervention could potentially provide a low-cost solution for a considerable subgroup of the population and may be a useful supplement for face-to-face programs. Given the success of such approaches to support smoking cessation[75] and recovery from depression,[76] it should in theory be possible to use them to support changes in diet and physical activity. Although a number of programs are under evaluation, more robust evidence on effectiveness is still needed before this approach can be endorsed.

TABLE 5-2 The FITT Recommendations: General Guidelines for Individuals of Moderate Fitness[38]

FITT PRINCIPLE		AEROBIC ENDURANCE TRAINING	RESISTANCE TRAINING
Frequency	How often	3 ×/wk (minimum) Max 2-day gap between training sessions	2-3×/wk
Intensity	How hard	(a) Light to moderate (40%-60% V_{O_2} max/50%-70% HRmax) (e.g., brisk walking—5-6 km/hr) Slightly increased breathing rate (b) Vigorous (e.g., jogging—8-10 km/hr) Increased breathing rate and sweating	Light to moderate (slight muscular fatigue)
Time	How long	(a) Light to moderate 45-60 min (total >150 min/wk) (b) Vigorous 30-40 min (total >90 min/wk)	One to three sets of 8-15 repetitions for each exercise
Type	What kind	Walking, jogging, cycling, swimming, hiking, skiing	Approximately eight different strength exercises using the major muscles of the body (e.g., with fitness machines, resistance bands, or just with your own body weight)

HRmax = Maximum heart rate as assessed by a cardiac stress test (or similar); V_{O_2}max = maximum rate of oxygen consumption as measured during incremental exercise testing.

TABLE 5-3 The EAT CLEVER Principle—Brief Practical Advice for Counselors to Be Applied Within the Framework of National Dietary Recommendations[38]

	EAT CLEVER
*E*stimation of the dietary pattern compared with the recommendations	Use the food diary or interview to help your patient become aware of his or her dietary pattern and food consumption. Compare dietary intake with the recommendations. Consider special needs, resources, and readiness to change food habits.
*A*ims in the long and short term	Discuss both short- and long-term goals: What is your patient willing and able to do at the moment? Help to set practical, achievable targets and proceed with small steps. Make a plan with your patient.
*T*ools, guidance, and support	What types of tools, guidance, support, or skills are needed and available? Involving the family and friends and participating in group counseling are worth considering.
*C*omposition of the diet	A diet high in sugar and other refined carbohydrates and low in fiber content or high in saturated and *trans* fats may increase the risk for diabetes and other related disorders. Whole grains and moderate amounts of coffee and alcohol may decrease the risk. Encourage the use of herbs and spices to reduce salt. Refer to national nutrition recommendations, but consider the special requirements of people with high diabetes risk, such as the improvement of the components of the metabolic syndrome. Take into account any additional disease the patient may have.
*L*ifestyle for the whole life	Diet is influenced by culture; religion; ethical, physiologic, psychological, social, and economic aspects; availability of food items; and individual likes and dislikes. Help the patient to find his or her own healthy way of life. Lifestyle change is a process and relapses are part of it. Help your patient to learn from these experiences to develop successful strategies over time.
*E*nergy	Excessive energy intake causes weight gain. If the patient is overweight, make a plan with her or him to support gradual weight loss (step by step). Focus on substituting foods with high saturated fat and/or refined carbohydrate content with lower-energy items. How many meals and snacks, beverages and alcohol included, does he or she have during a day and night? Some regularity in the daily meal plan helps to control over-eating.
*V*ariety	Emphasize variety instead of restriction. A health-promoting diet provides satiety and pleasure as well as protective nutrients. Encourage patients to try new foods. Give advice on how to read food labels. This can help your patient to feel more confident and expand his or her healthy food choices.
*E*valuation	Evaluation and self-monitoring help in achieving and maintaining new food habits. Body weight and/or waist circumference should be measured regularly. Encourage your patient to use a food diary or some other methods to monitor eating habits: the number of meals and snacks, the amounts of certain food stuffs, such as vegetables, whole grains, sugar, alcoholic beverages, vegetable oil and/or fat, and so on.
*R*isks management	Dietary guidance must be based on evidence from nutrition and behavioral sciences. Focus on the big picture: Changing one aspect in the diet affects many others. Strict restrictions and "crash dieting" may lead to an unhealthy diet, and can cause damage in the long term as well as psychological and social harm. A multidisciplinary team, including a registered dietitan and a psychologist, can give essential support to avoid these risks.

- *Developing standardized recommendation for diabetes prevention practice.*[37,38] Applying the recommendations on supporting behavior change should enhance the efficiency of lifestyle intervention programs.
- *Disclosing the economic benefits of diabetes prevention.*[77] Economic modeling indicates that group-based diabetes prevention interventions in the United States would provide a return on investment within a 3-year time frame. This has resulted in the release of significant resources in the United States from government and health maintenance organizations.
- *Taking advantage of expertise.* To deliver prevention programs on a large scale, we need to identify a sufficient number of people with the expertise and experience to

BOX 5-1 Nutrition and Dietary Guidance for Sustained Diabetes Prevention[38]

GOALS FOR FOOD INTAKE	GOALS FOR LONG-TERM NUTRIENT INTAKE
• Consuming fruit, vegetables, and legumes in abundance (≥500 g or five portions per day) • Choosing whole grains in all cereal products • Limiting sugar to ≤50 g/day, including sugar in food and beverages • Consuming vegetable oil and/or soft margarines and/or nuts as the primary source of fat • Limiting butter, other saturated fat, and partially hydrogenated fats • Choosing low-fat milk and meat products • Consuming fish regularly (≥2 times per week) • Consuming alcoholic beverages in moderation (≤2 drinks/day for men and ≤1 drink/day for women) if at all • Other goals according to individual needs (e.g., body weight, diseases, medications, age)	• Energy intake balanced with physical activity levels to achieve or maintain healthy body weight • Total fat 25 to 35 E%* (60 to 80 g/day with 2000 kcal daily intake level), of which saturated or trans fat is 10 E% or less • Dietary fiber 25 to 35 g/day • Salt (NaCl) ≤6 g/day • Alcohol ≤5 E%*

*E% = Proportion of total energy.

design and deliver them. Investing in high-quality training would seem to be essential for the implementation of successful programs.[71]

- *Maximizing the uptake of both screening and intervention.* Further research is needed in this area, but this may require multimedia approaches, involvement of multiple sectors (public health, voluntary sector, commercial and workplace programs, health care, and social care), and the use of social marketing techniques to target messages to appropriate population subgroups.
- *Ensuring sustainability of funding and support within both health care and political arenas.* This will require a sustained focus and willingness to invest in preventive health care. The United Nations summit on noncommunicable diseases has helped to present an opportunity to more firmly and sustainably establish diabetes prevention on the global health agenda.[78]
- *Developing quality management systems.* Quality management systems are needed to provide continuous benchmarking and monitoring of the effectiveness of prevention programs.[70]
- *Further improving the technology to support behavior change.* This could be achieved by establishing "networks of practice" so that we can learn how to improve the efficiency of interventions from practice or real-world experience as well as from developments in theory and research. The global network Active in Diabetes Prevention (www.activeindiabetesprevention.com) provides a forum for exchanging knowledge and intervention materials as well as educational standards and recommendations for prevention practice.

Improving Effectiveness in Type 2 Diabetes Diabetes Prevention Practice

One of the challenges in developing intervention programs for diabetes prevention is to find the right intervention that has the highest probability to be successful in the individual with high T2DM risk. This strongly varies among different individuals. In today's practice, we should aim to be using standardized and structured intervention programs that we apply to all the people at risk that we have identified in a prevention plan. By this approach, we accept that sometimes only 20% of the people achieve the highest effect and that in 80% of the people the program may be less efficient.[79] It is possible to increase the probability of success by developing intervention programs that follow a behavior change model. Such a model was developed as part of the IMAGE project, wherein patients are seen as being in three stages[37,66]:

- The stage of motivation
- The stage of action
- The stage of maintenance

The development of intervention programs following this behavior change model may generate a higher efficacy because of an increase in flexibility in program execution (see also **Chapter 12**). The key point in the IMAGE project was that the behavior change model was accompanied by a collection of behavioral techniques for supporting the lifestyle changes (see **Fig. 5-2**). Specific tools and techniques for each stage of the behavior change model were elicited from more than 300 studies[66] and shown to be effective. The prevention manager can choose the techniques needed for the intervention in several stages. The use of the techniques allows a much more widespread implementation of an intervention plan and may be one step away from focusing only on structured and standardized intervention concepts by allowing a higher degree of flexibility of the intervention manager and focusing more on individual needs and preferences.

This behavior change model then was further developed by a working group derived from the IMAGE project.[18,66] Daily practice in performing intervention shows that even the intervention planning, by focusing on the behavior change model, misses an effect in a large number of people receiving the intervention. One of the difficulties is associated with the use of standardized programs that follow a standardized curriculum. Furthermore, difficulties also arise from the fact that most of the intervention programs do not include different preferences and interests of the people receiving the intervention. This is followed by different stages of morbidity[81] that also define different preferences and interests that can be a barrier to an effect of a program if someone with very low risk is sitting together in an intervention group with someone having a very high risk and different preferences and interests. Based on this background, the further development of intervention programs must take this information into account to develop an assessment to identify the most suitable intervention characteristics for a person at risk.

Prevention Managers

As part of the IMAGE project, a curriculum for the training of prevention managers was also developed.[71] The purpose was to develop common European learning goals, teaching methods, and contents as well as teaching material for the training of health care professionals who want to carry out lifestyle interventions for T2DM prevention (Prevention

Managers T2DM). With this curriculum, for the first time, standardized state-of-the art training for health care professionals interested in offering preventive intervention can be performed Europe-wide in a comparable and consistent way. This is particularly useful because a standardized method to train the trainers for T2DM prevention can also pilot the same strategies for the prevention of other chronic diseases. All materials needed to train a prevention manager are freely available at www.virtualpreventioncenter.com. National institutions, such as universities or associations interested in the training of eligible health care professionals, are encouraged to download the specific teaching materials and follow the curriculum for the training of prevention managers.

The idea behind the curriculum for the training of diabetes prevention managers was to develop a standardized training curriculum for people coming from different professional disciplines who together want to deliver coordinated interventions for the prevention of T2DM. Currently 11 European countries and more than 20 extra-European countries have started to train prevention managers following the IMAGE curriculum.

MOVING DIABETES PREVENTION INTO PRACTICE

A challenging step is to translate the research findings into nationwide or regional diabetes prevention programs that translate the research findings to real-life health care settings. Finland has led the way with FIN-D2D, a large-scale implementation covering a quarter of the Finnish population.[82] Another landmark was the profusion of published implementation trials including Good Ageing in Lahti Region (GOAL) and the Saxon Diabetes Prevention Program in Europe,[83] the Greater Green Triangle Diabetes Prevention Project in Australia, the Walking away from Type 2 Diabetes program in the United Kingdom,[81,84] and programs in Indianapolis, Pittsburgh, and Montana in the United States.[4,85] A great challenge will be the scaling up from these implementation trials to sizeable regional and national programs.

Political support is needed, and this requires the development of a national or international action plan for diabetes prevention, which needs involvement of a number of stakeholders at governmental and nongovernmental levels. Furthermore, the presentation of the evidence in the field of diabetes prevention on the scientific and practical level as well as the training of people to deliver preventive intervention are required.

Steps in Development of a Prevention Program

Basic Science in Diabetes Prevention

Exploration of the molecular physiology of the prevention of T2DM is key to both understanding the pathobiologic mechanisms of diabetes prevention and also developing targeted intervention programs with improved outcomes. Growing evidence suggests that insulin resistance in a normoglycemic person is the key processor of the development of T2DM risk (see also **Chapter 2**).[30] The role of visceral fat mass and visceral obesity seems to be a key trigger for the development of insulin resistance (see also **Chapter 6**).[87] The visceral fat secreted adipokine profile directly influences inflammatory processes and insulin resistance development, which then altogether directly influence diabetes risk.[88] Furthermore, increasing levels of circulating insulin and proinsulin seem to be a major factor in triggering T2DM development and subsequent cardiovascular disease and cardiovascular morbidity. Understanding these pathophysiologic mechanisms will make it necessary to explore the genetic basis of the regulation of insulin resistance and to understand visceral obesity and the combined pathophysiology behind it. Current evidence from genome-wide association studies explains a small proportion of T2DM pathophysiology (see also **Chapter 2**).[89,90] However, current investigations suggest that there is a link between genetic susceptibility and the outcome in preventive interventions.[91,92] Furthermore, results from basic prevention studies show that there is a substantial proportion of people at risk for T2DM who do not respond to an intervention or do not benefit from an intervention, even without T2DM development. A significant challenge in the future is development of pathophysiology-targeted prevention programs, as well as identification of nonresponders to preventive interventions.

Efficacy in Diabetes Prevention

To test intervention concepts and to generate evidence about intervention structures, T2DM prevention programs have to be tested in ideal RCT settings. In recent years considerable evidence has shown that sustained lifestyle change enables a significant ability to prevent or delay T2DM.[15,93] A number of large randomized clinical trials have shown that interventions focusing on improved physical activity and nutritional intake along with strategies and supports for behavior change enabled up to 58% prevention of T2DM. Furthermore, use of traditionally known diabetes drugs enables prevention of T2DM (see also **Chapter 6**).[15,27] Lifestyle interventions and drug treatment do not show an additive effect; unfortunately, there is conflicting evidence about the combination. Lifestyle intervention was more effective in older adults and less effective in obese people than the drug metformin. Metformin was more effective in younger, heavier people and women with a history of gestational diabetes mellitus (GDM) in the DPP.[15] By summarizing the efficacy of interventions for diabetes prevention, we have learned that the prevention of diabetes is effective and feasible, but we have also identified barriers and the challenging task of how to implement this knowledge.[94]

The efficacy of diabetes prevention programs may be strongly influenced by pathophysiologic differences. There is a huge variation in the conversion from IGT to T2DM, and the trigger mechanisms are not completely understood. The higher the conversion rate is, and the higher the prevalence of impaired glucose metabolism in the population, the greater the efficacy of prevention programs. Because the prevalence of IGT is increasing in almost all populations, the efficacy of T2DM prevention programs may increase in the future.[18]

Effectiveness in Diabetes Prevention

After evidence has been obtained from RCTs, it is necessary to translate this knowledge into real-world settings. This generates a number of new challenges and makes it necessary to start a critical discussion about necessity and practicability of what was done in the RCTs and what is applicable to real-world settings. A number of translation studies have tried to do this and have found ways to reduce costs and achieve the same or similar weight loss as in the RCTs. There are challenges in moving from RCTs to real-world

implementation in diabetes prevention. One issue is screening to identify individuals at high risk. It is unrealistic to believe that performing two oral glucose tolerance tests for screening, which is done in some countries, can be appropriate for prevention programs in real-world settings, except in very high-risk individuals in the medical environment. A number of translational trials have been performed in several parts of the world, with different experiences. The implementation design often depends on limited financial resources and is driven by the circumstances in the environment to enable screening and intervention. Therefore the translational trials are often driven by the practical need for diabetes prevention and the dimensions of the clinical and public health problem in the environment. They adjust screening procedures and interventions to fit the existing environments, driven by the hypothesis to test the feasibility and applicability of an intervention program to the real-world setting.[40] The subsequent translation studies of the U.S. DPP have shown that by delivering the program in a group setting (instead of one-on-one) and using lower-cost trained health educators and community organization staff, the program can be delivered effectively and cost-effectively.[95]

Efficiency of Diabetes Prevention

After having learned from the implementation trials and having put together practical evidence from effectiveness studies, the next challenge is to modify the programs or their implementation to achieve the biggest impact for the most people who need the intervention. The efficacy research studies are often applicable only to a limited part of the population, and studies often include a relatively small number of people. The effectiveness trials are more likely to use a more broadly defined high-risk population, but the interventions that have been proven to be effective in real-world settings still may not address factors that will scale the intervention to reach the most people. At this stage, for the first time, policy perspectives and plans for cost-effective expansion of the intervention are taken into account. RCTs or effectiveness trials cannot tell us how to achieve the best effect for most of the people; this requires networking with a number of specialists and stakeholders from neighboring fields in medicine and public health and with expertise in fields such as management, economics, and policy development.

For programs to be efficient in the prevention of T2DM on a population level, political support on local and national levels to build national diabetes prevention plans is needed. These plans help relevant players and stakeholders to network to agree on a concerted plan of action involving different societal and personal resources to enable an efficient and wide-reaching T2DM prevention program.

Availability of Diabetes Prevention

After the efficiency of T2DM prevention has been addressed through a practical framework of stakeholders, and with political support and the necessary resources to enable a population-based impact, it is necessary to address program availability, accessibility, and capacity. Availability includes an adequate number of programs with easy access in the community, the existence of adequate personnel resources to train the prevention managers, and an adequate number of prevention managers. The development of the European curriculum for the training of prevention mangers is a relevant achievement to standardize intervention procedures and to develop "train the trainer" strategies. As part of the National Diabetes Prevention Program, the United States has developed the Diabetes Training and Technical Assistance Center at Emory University to help train master trainers and lifestyle coaches and coordinate training efforts.[95] Policies that support adequate resources and coordination are important at this stage and support from scientists and medical experts in the field to drive the right political decisions and program availability is vital.

The industrialization of T2DM prevention programs becomes a relevant challenge. The Danish example of the tax on saturated fatty acids is an effective model for T2DM prevention on a national scale, but the intervention failed because of political reasons and the missing pan-European policy. The industrialization can also be achieved by adequate and intensified training of medical professional and health care workers to conduct T2DM prevention programs and to build a framework to implement business solutions for T2DM prevention. The extensive growth of new media and mobile health solutions may help to make healthy lifestyle information more available throughout the population, but also to enable mobile health intervention concepts. We have to accept that no one solution will address the needs of a large population. We will need a number of solutions providing adequate care and attention for T2DM prevention, based on target populations, individual prevalence, readiness to change lifestyle, environmental and regional aspects, and many more factors.[18]

Distribution of Diabetes Prevention

Even the best program will fail if it cannot reach people at increased risk.[83] Any preventive action will have to be performed in the environment in which the people at increased risk live and work.[3,96] Structures and policies to identify high-risk individuals and manage intervention follow-up and evaluation have to be established. Scientific evaluation standards based on the RCTs need to be translated into the public health care setting with careful management of considerably more limited resources. This has been achieved in Europe by the international IMAGE consortium with a quality management structure.[70] In the United States, the National Diabetes Prevention Program includes a recognition program that sets standards that help ensure program quality and consistency. The U.S. Centers for Disease Control and Prevention (CDC) is responsible for conducting this program and reporting on the distribution and quality of the diabetes prevention program across the United States.[95]

National Initiatives

Along with European level support, national governments and health care organizations are increasingly developing tailored national policies and guidance aimed at the prevention of chronic disease. For example, Finland has adopted a regional systematic whole-system approach across all sectors of the health care community, including primary care, pharmacy, and community settings, to the prevention of T2DM.[82] In the United Kingdom, the National Health Service Health Check program has been rolled out nationally and aims to screen all individuals aged 45 to 70 years for the risk of chronic disease and to treat high-risk individuals accordingly (www.healthcheck.nhs.uk).[86] In addition, new NICE guidance has been published that provides a blueprint for the prevention of T2DM in the community and primary care.[33] A similar program is under way in Germany. A health check for which all



persons aged 35 to 65 years are eligible will be established including FINDRISC scoring, parameters of the metabolic syndrome, HbA1c, and creatinine. For persons determined on screening to be at risk, standardized management will be established to place them into primary and secondary prevention programs; newly identified T2DM patients will be included in disease management programs.

In November 2011, Denmark introduced a tax on saturated fatty acids: 1 kg saturated fatty acids increased taxes by 2.50 €. This has successfully reduced the sales of products with a high content of fat significantly. Unfortunately, after 11 months, Denmark postponed the tax as a result of disruption of national business, because Danish people tended to cross country borders to shop in Germany. Both examples show that standardized guidelines and summarized evidence alone do not foster the implementation of T2DM prevention programs. National initiatives are the key to targeting people at high risk and can be models for success on a regional, local, or national level. Population-based strategies, for example, including taxes on unhealthy food, require pan-national policies and activities but can be very efficient with regard to effects on the overall public health of a population.

Fulfilling the Development of a National Diabetes Prevention Program

Within the European Union, only five of 27 countries have a national diabetes plan, and only one has a national diabetes prevention program.[97] In Asia the situation is similar, with a progressive increase in the number of countries including diabetes prevention in their national policies.[98] The United States is at the forefront of governmental initiatives for developing a diabetes prevention program, with the CDC being the driving force for coordinating the national effort.[95] The existence of a national policy for supporting diabetes prevention does not always equate with a positive outcome, but it is a mandatory first step for successful public health implementation. The European Coalition for Diabetes, together with the EU Diabetes Working Group, has installed working groups to address the need for delivering adequate care for diabetes in Europe. Those working groups have elaborated recommendations to the EU institutions and other governments to take urgent action to address the major public health challenge that diabetes represents. Currently in Germany and England, national programs for identifying people at high risk are in development, based on the German Check-up 35+ program and the English NHS Health Checks program. However, nationally available lifestyle based prevention programs to treat people at high risk are still needed.

For prevention of T2DM, an adequate scientific basis provided by research, efficacy studies in highly controlled environments, and effectiveness studies in real-world environments performed by clinical researchers and public health experts are necessary. To scale up the delivery of T2DM preventive actions to the population, the program strategies, as well as the supply and diffusion of the intervention into the population, have to be adjusted to have the best effect for a relevant proportion of the population. Policy development is a necessary precursor to the development of national prevention programs. The development of national T2DM prevention and management plans, which are developed in consultation with local prevention managers, service users, and commissioners, is necessary to guide implementation of diabetes prevention at a population level.[4]

SUMMARY

T2DM prevention is a major opportunity for global health, and some have even referred to it as "the future of diabetology." The evidence that T2DM is a preventable disease is excellent. A number of large randomized clinical trials have shown that more than 50% of T2DM risk can be reduced, and T2DM can be postponed and prevented sustainably over more than a decade. Studies that translated scientific evidence into clinical practice have proven that similar results are achievable in clinical practice and that it is feasible to implement T2DM prevention programs in different care processes and structures. However, these translational studies also have shown that it is the responsibility of health care policies to harness existing care structures and infrastructure to develop and support the prevention programs and to ensure the desired outcomes for the persons at risk and the community. Over recent years, we have learned much about nonpharmacologic interventions and that they are effective in preventing T2DM, and we have gained much knowledge regarding policies that still need to be developed.[18] Effective strategies to identify people with increased T2DM risk are available. Changing physical activity levels and eating habits can be effective in the prevention of T2DM.

Now we have to carry the ball from the research arena into the political field. Political support is needed to build the framework for successful implementation of diabetes prevention programs. Ultimately, together with all relevant stakeholders, we have to build effective and sustainable prevention programs. There is no longer an excuse for policy makers and health care providers to delay taking action to prevent type 2 diabetes. As Kofi Annan said, "…we do not have enough money not to act."

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6 Pharmacologic and Surgical Interventions That Prevent or Worsen Type 2 Diabetes



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Detection of individuals at risk of future diseases and implementation of programs to reduce risk of progression to disease are fundamental objectives of reducing the burden of medical conditions such as diabetes. Prevention of diabetes also offers the opportunity to reduce the risk of cardiovascular disease (CVD), which is the major cause of premature death and chronic disability in patients with type 2 diabetes.

CVD risk factors rarely exist in isolation and frequently occur in combination with conditions such as diabetes.[1] A study of 371,221 outpatients reported that 30.7% had hypertension and dyslipidemia, and 10.7% had concomitant diabetes.[2] In another observational study, among 420 patients with hypertension, abnormal glucose metabolism was documented in 68.5%, insulin resistance in 9.3%, impaired glucose tolerance in 22.5%, and diabetes in 13.9%.[3] Comorbidity with hypertension, coronary artery disease (CAD), or heart failure is also common in patients with type 2 diabetes. Vascular insulin resistance contributing to endothelial dysfunction deteriorates glucose supply and thereby usage in peripheral tissue. Vascular insulin resistance may therefore be an important factor in treating patients with type 2 diabetes or features of the metabolic syndrome.

The pathogenesis of type 2 diabetes involves both multiorgan insulin resistance and inadequate insulin secretion by pancreatic beta cells, leading to fasting and postprandial hyperglycemia. Normal glucose tolerance requires an appropriate integration of the metabolic response to an oral glucose challenge (**Box 6-1**). All of these components are usually defective in patients with type 2 diabetes.[4,5] The average length of time between the onset of beta cell dysfunction and the development of overt type 2 diabetes is 10 years.[6]

Insulin also activates the sympathetic nervous system (SNS), resulting in an increase in cardiac output, blood pressure, and delivery of insulin and glucose to the peripheral tissues.[7] Insulin resistance is associated with increased SNS and renin-angiotensin-aldosterone system (RAAS) activation. RAAS overactivity stimulates angiotensin receptors, impairing vascular and skeletal muscle tissue insulin signaling.[7] Diabetes has an asymptomatic preclinical phase; hence, in the absence of routine screening, a significant proportion of individuals with diabetes remain undiagnosed. Type 2 diabetes continues to increase in prevalence, but the frequency of its occurrence varies by ethnicity.[8–10] Studies from the United States have shown a higher incidence and prevalence of type 2 diabetes in Hispanic, Asian, and black patients compared with white patients.[11–13] Also, the prevalence of undiagnosed diabetes in the general population increases with age, is higher in men than in women, and is higher in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites.[14–17] Similarly, economic studies indicate that cost is elevated before the onset of clinical disease.[18,19] In 2007 in the United States, the economic cost of undiagnosed diabetes was estimated to be $18 billion, or $2864 per person with undiagnosed diabetes.[20,21] This estimate includes $11 billion in medical costs and $7 billion in indirect costs.[20,21] The risk of developing type 2 diabetes increases linearly with body mass index (BMI).[22,23] Accordingly, the increase in the prevalence of obesity is likely responsible for the recent increase in type 2 diabetes, which has become a major global health problem because of its high prevalence, causal relationship with serious medical complications, and economic impact. It is therefore important to better understand what and how pharmacologic and surgical treatments may positively or negatively affect glucose metabolism in individuals at high risk of developing type 2 diabetes (**Box 6-2**).

BOX 6-1 Parameters Associated with a Normal Glucose Response

- Appropriate increase in insulin secretion
- Insulin-mediated suppression of endogenous (primarily hepatic) glucose production
- Insulin-mediated stimulation of glucose uptake
- Use by peripheral tissues (primarily skeletal muscle)

BOX 6-2 Pharmacologic Therapy That Influences Glucose Metabolism

Favorable
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Vasodilating beta blockers
Potassium supplementation or concomitant use of potassium-sparing agents
Ezetimibe
Bile acid sequestrants
Fibrates

Neutral
Calcium channel blockers

Unfavorable
Nonvasodilating beta blockers
High-dose thiazide diuretics
Statins
Niacin

CARDIOVASCULAR PHARMACOLOGIC TREATMENT THAT INFLUENCES GLUCOSE METABOLISM AND THE DEVELOPMENT OF DIABETES

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

It is not clear that a reduction in diabetes incidence through the RAAS blockade pathway observed in a number of randomized trials represents a truly preventive effect or simply a delay or a masking effect (**Table 6-1**). Overall, diabetes incidence was not a prespecified, primary endpoint in any of these prior studies, and there was insufficient evidence to definitively recommend any given angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients at risk of developing type 2 diabetes for the purpose of diabetes prevention. Nevertheless, in the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitor therapy with ramipril lowered diabetes incidence from 5.4% to 3.6% overall, and in the Studies of Left Ventricular Dysfunction (SOLVD) trial of patients with systolic heart failure, enalapril reduced diabetes incidence from 22% to 6%.[24,25] The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study reported a significant reduction in the incidence of type 2 diabetes from 11.5% to 9.8% in patients with stable CAD treated with trandolapril.[26] ARB therapy significantly decreased diabetes incidence in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study from 7% to 6% and resulted in a nonsignificant decrease in diabetes incidence from 5.3% to 4.3% in the Study on Cognition and Prognosis in the Elderly (SCOPE) trial.[27,28] In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial of 10,419 hypertensive patients at high cardiovascular risk, a valsartan-based treatment regimen was associated with a decrease in the incidence of type 2 diabetes from 16% to 13% compared with an amlodipine-based regimen.[29]

TABLE 6-1 Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Diabetes Incidence

NAME OF TRIAL	REDUCTION IN INCIDENCE OF DIABETES
Heart Outcomes Prevention Evaluation (HOPE)	5.4% to 3.6%
Studies of Left Ventricular Dysfunction (SOLVD)	22.0% to 6.0%
Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE)	11.5% to 9.8%
Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)	7.0% to 6.0%
Study on Cognition and Prognosis in the Elderly (SCOPE)	5.3% to 4.3%
Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)	16.0% to 13.0%

There are several potential mechanisms by which ACE inhibitors or other pharmacologic therapies may exert beneficial effects on glycemic control (**Fig. 6-1**). The activation of the SNS via alpha$_2$-adrenergic receptors impairs insulin secretion and peripheral glucose uptake.[30] Inhibition of the SNS via inhibition of angiotensin II production counteracts this effect. Also, angiotensin II impairs pancreatic blood flow and enhances insulin resistance. However, this pathophysiologic pathway has not been a consistent finding across studies. Angiotensin II also mediates a number of potentially toxic effects within the pancreas, such as islet cell fibrosis and death, oxidative stress, impaired first-phase insulin release, and cytokine release.[31] ACE inhibitors also directly improve insulin sensitivity, primarily in skeletal muscle. This appears partially mediated through the vasodilatory actions of the upregulation of bradykinin and nitric oxide. Inhibition of the RAAS system also may augment the postreceptor activity of insulin,[31] and angiotensin II has also been shown to inhibit adipocyte differentiation in vitro.[32,33] Through this latter mechanism, ACE inhibition may improve insulin sensitivity through promotion of adipocyte differentiation, yielding increased storage depot for caloric excess. Furthermore, inhibition of the RAAS pathway increases adiponectin and leptin levels, both of which increase insulin sensitivity and promote adipocyte differentiation.[33] ACE inhibitors also raise circulating potassium levels, which counteracts the impairment in insulin secretion seen with hypokalemia. With the exception of effects mediated through the upregulation of bradykinin, all of these potential mechanisms are, in theory, also applicable to ARBs. In addition, telmisartan, a partial agonist of the peroxisome proliferator-activated receptor gamma (PPAR-γ), may lower glucose levels in a similar fashion but with less efficiency, compared with the thiazolidinedione medications.[34]

Beta Blockers

Beta blockers, which decrease SNS activation via beta-adrenergic receptor antagonism, are effective in reducing cardiovascular morbidity and mortality in patients with several conditions, including those who have sustained a myocardial infarction and those with systolic heart failure.

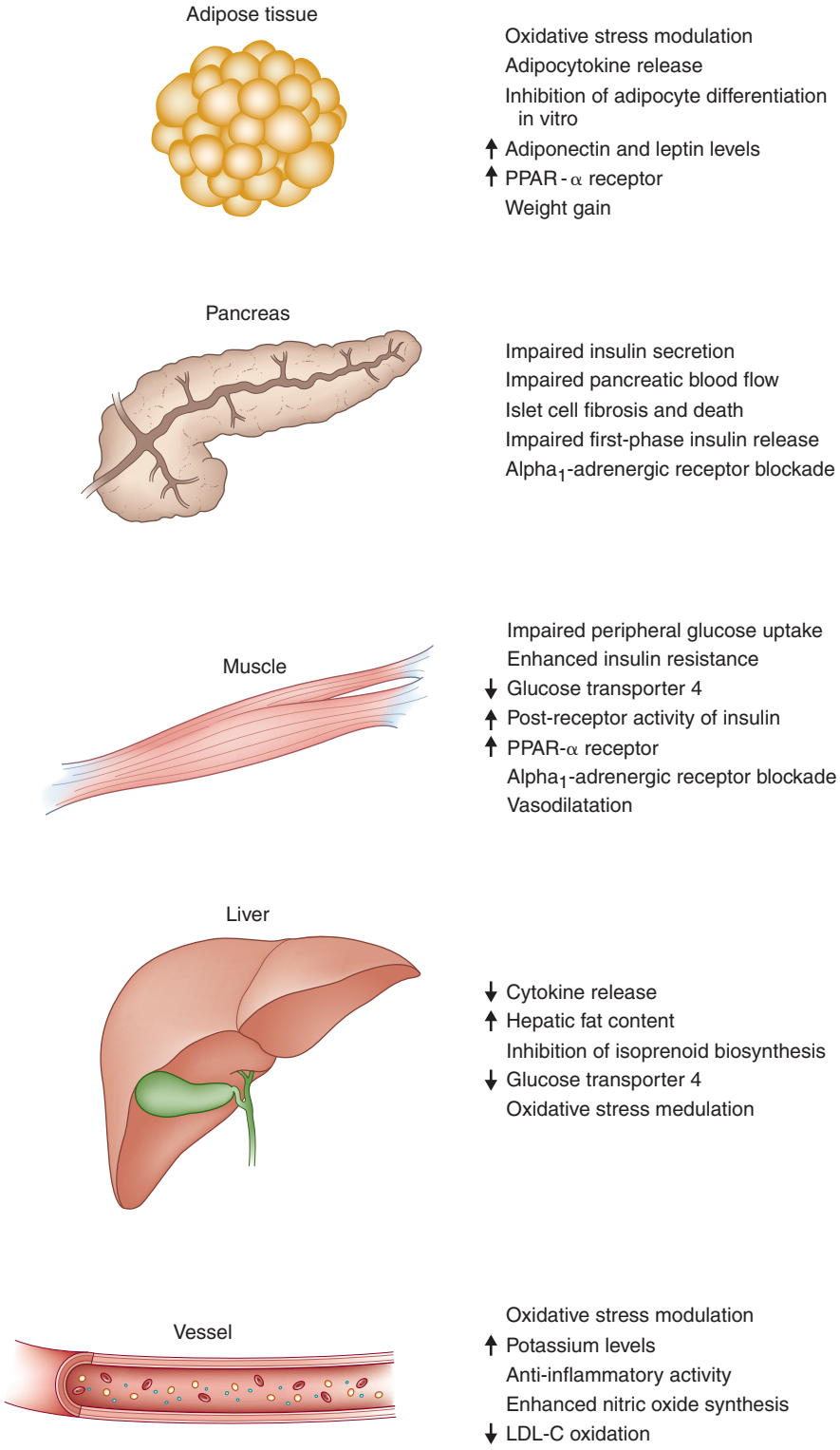


FIGURE 6-1 Potential mechanisms by which pharmacologic therapies may affect glycemic control. LDL-C = Low-density lipoprotein cholesterol; PPAR-α = peroxisome proliferator-activated receptor alpha.

Despite these clinical benefits, many physicians are reluctant to prescribe beta blockers because of perceived negative metabolic effects (**Box 6-3**). However, beta blockers should not be considered a homogenous class of agents. Beta blockers consist of nonvasodilating and vasodilating agents, which differ in terms of their mechanisms of action and effects on glucose and lipid metabolism. Treatment with nonvasodilating beta blockers is associated with an increased propensity of patients with hypertension to develop diabetes. A substudy of the Atherosclerosis Risk in Communities (ARIC) observational cohort study, which included 3804 patients with hypertension, demonstrated that patients treated with nonvasodilating beta blockers had a 28% higher risk of developing diabetes than patients on no pharmacologic treatment for hypertension.[35] Patients receiving thiazide diuretics, ACE inhibitors, or calcium

BOX 6-3 Potential Deleterious Metabolic Effects of Beta Blockers

- Reduced glycemic control
- Masking of hypoglycemia
- Deterioration in insulin resistance
 - Decreased blood flow to muscles, reducing peripheral insulin-stimulated glucose uptake
 - Interference with insulin secretion from pancreatic beta cells
 - Decrement in the first phase of insulin secretion
- Weight gain
- Dyslipidemia

channel antagonists were not at significantly higher or lower risk for subsequent diabetes than untreated patients.[35] Similarly, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) randomized trial demonstrated in 9193 patients that the risk of developing diabetes was 25% lower among patients with hypertension and left ventricular hypertrophy who received losartan- based therapy than among patients who received atenolol-based therapy.[36]

Nonvasodilating beta blockers (atenolol, metoprolol, pindolol, and propranolol) reduce blood pressure in association with a cardiac output reduction and may increase or have no appreciable influence on peripheral vascular resistance.[37] Nonvasodilating beta blockers include first- and second-generation agents. First-generation beta blockers (propranolol) block both $beta_1$- and $beta_2$-adrenergic receptors (nonselective beta blockade), whereas second-generation beta blockers (atenolol and metoprolol) specifically target $beta_1$-adrenergic receptors (cardioselective beta blockade).[38] Nonvasodilating beta blockers significantly decrease insulin sensitivity by approximately 14% to 33% among patients with hypertension.[39,40] Studies have shown increases in glucose concentrations with the use of atenolol alone,[41,42] metoprolol,[43] or propranolol,[44,45] although other studies have shown no changes in glucose levels with atenolol[46–48] or propranolol.[49,50] However, glucose levels at a particular timepoint may not reflect long-term changes in glucose metabolism as reflected by hemoglobin A1c (HbA1c). As an example, after 6 months of treatment, once-daily metoprolol did not affect fasting plasma glucose but significantly increased HbA1c levels by a relative increase of 5% from baseline in patients with hypertension.[51]

In contrast, vasodilating beta blockers (carvedilol, labetalol, and nebivolol) reduce peripheral vascular resistance but have little or no effect on cardiac output. Numerous studies have shown that vasodilating beta blockers are associated with more favorable effects on glucose and lipid profiles than nonvasodilating beta blockers.[52] Bisoprolol, a $beta_1$-selective adrenergic blocker, was reported to have a neutral effect on glucose and insulin levels during a glucose tolerance test after 24 weeks of treatment at 5 to 10 mg/day in 13 patients with hypertension.[53]

Although the specific mechanisms have not been identified, several have been postulated to explain the negative effects of nonvasodilating beta blockers on glucose and lipid metabolism, most of which relate to their hemodynamic effects. Treatment with nonvasodilating beta blockers, which block either the $beta_1$-adrenergic receptor or the $beta_1$- and $beta_2$-adrenergic receptors, results in unopposed $alpha_1$-adrenergic receptor activity (which can induce vasoconstriction), decreased blood flow to the muscles, and reduced insulin-stimulated glucose uptake in the periphery.[54,55] Nonvasodilating beta blockers may also interfere with insulin secretion from pancreatic beta cells. Moreover, beta blockers may decrease the first phase of insulin secretion (potentially an important predictor of diabetes) via impairment of $beta_2$-mediated insulin release.[54,56] Weight gain also has been noted in patients who received nonvasodilating beta blockers[57,58] and is closely linked to an increased risk for developing diabetes.[59] Increased peripheral blood flow from the action of vasodilating beta blockers may result in efficient glucose dispersal to the skeletal muscles, thereby facilitating insulin sensitivity.[37] The mechanisms responsible for the beneficial effects of vasodilating beta blockers on glucose and lipid metabolism are not entirely understood but may include $alpha_1$-adrenergic receptor blockade, vasodilation, reduced oxidative stress, anti-inflammatory activity, and lack of weight gain.[52,60,61]

In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, the metabolic effects of carvedilol and metoprolol were compared in 1235 patients with type 2 diabetes and hypertension. The use of carvedilol in the presence of RAAS blockade was not deleterious to glycemic control and improved some components of the metabolic syndrome relative to metoprolol.[62] On the other hand, metoprolol significantly increased HbA1c levels from baseline (absolute increase of 0.15%), in contrast to carvedilol (0.02%) with an absolute difference between the groups of 0.13% ($P=0.004$ for carvedilol versus metoprolol).[62] Statistically significant improvement was observed in insulin sensitivity with carvedilol (−9.1%) but not statistically significant with metoprolol (−2.0%). In this trial, metoprolol-treated patients experienced a significant weight gain (1.2 ± 0.16 kg) compared with carvedilol-treated patients (0.17 ± 0.19 kg).[63] In another study, a group of patients treated with metoprolol had an increase in body weight of 1.8 kg after 2 months of treatment. In contrast, no significant weight gain was found in the group of patients treated with carvedilol.[64] This is in accordance with the weight gain seen after treatment with beta blockers in large clinical trials.[65] In the presence of heart failure, carvedilol was shown to be associated with improved survival (the Carvedilol or Metoprolol European Trial [COMET]) and with fewer cases of new-onset diabetes compared with metoprolol.[66,67]

Carvedilol and nebivolol enhance nitric oxide synthesis and thus mediate endothelial-dependent vasodilation.[68–71] Carvedilol is associated with antioxidant activity, possibly because of stimulation of endothelial nitric oxide production or reduced nitric oxide inactivation.[72,73] Carvedilol also inhibits low-density lipoprotein cholesterol (LDL-C) oxidation, potentially reducing the accumulation of oxidized LDL-C in vessel walls and subsequent vascular damage.[74] Furthermore, carvedilol has been shown to protect against reactive oxygen species via scavenging of free radicals, suppression of free radical generation, and prevention of ferric ion-induced oxidation.[72,73] Carvedilol treatment reduced proinflammatory markers, including plasma C-reactive protein and monocyte chemotactic protein 1, in patients with hypertension and diabetes.[73]

Nebivolol is considered to have a neutral effect on metabolic parameters in patients with hypertension,[7] but among 80 patients with hypertension, nebivolol significantly reduced baseline insulin levels and insulin resistance versus metoprolol after 6 months of treatment.[75] In a larger, open-label study involving 328 patients with hypertension, compared with baseline, nebivolol significantly reduced fasting



glucose, total cholesterol, and triglyceride levels.[76] Another large, open-label study involving 2838 patients with hypertension and diabetes showed that after 3 months of nebivolol treatment, significant reductions were observed from baseline in fasting glucose, HbA1c, total cholesterol, LDL-C, and triglyceride levels, with an increase in high-density lipoprotein cholesterol (HDL-C).[77] Several small studies have demonstrated that labetalol treatment compared with other antihypertensive therapies is associated with neutral effects on glucose and lipid metabolism in patients with essential hypertension.[78,79]

Thiazide Diuretics

Thiazide diuretics can result in various undesired biochemical changes, and in general increase glucose and insulin resistance. Thiazides have been shown to increase fasting glucose levels and impair glucose tolerance curves in many long-term studies.[80–82] The effect on glucose tolerance is usually reversible if the thiazide is stopped,[83] and the effect on blood glucose levels is dose related.[83]

The mechanistic underpinning of these effects is not well understood. Thiazide-induced hypokalemia, as well as effects on other pathophysiologic pathways, may explain these metabolic disturbances, such as increased visceral adiposity, hyperuricemia, decreased glucose metabolism, and pancreatic beta cell hyperpolarization.[84] Whereas many large randomized, prospective clinical trials show an association between thiazide use and increased blood glucose, findings are mixed regarding the association with new-onset diabetes. Many issues must be considered in evaluating these associations in these trials, including the following:

- Most are post hoc findings and were not adequately powered to assess this association.
- New-onset diabetes was defined differently in many studies.
- Many studies had follow-up durations of only a few years, which may not be long enough to fully assess prolonged hyperglycemia.
- Comparing drug classes is difficult because of differing study designs.[85]

A meta-analysis of clinical trials revealed that of all antihypertensives assessed, beta blockers and thiazide diuretics are associated with the highest risk of diabetes. This analysis found that thiazides are associated with higher risk of diabetes than placebo and, along with beta blockers, had the highest risk of all major classes of antihypertensives.[86] The pathophysiologic process accounting for these effects may be mediated through influence on potassium balance and circulating potassium levels. It has been reported that potassium infusions causing more than a 1- to 1.5-mEq/L elevation in plasma potassium enhance insulin release twofold to threefold compared with basal levels.[87] The relationship between potassium and glucose homeostasis is central because many believe that thiazide-induced potassium depletion drives hyperglycemia.[88] Actually, a meta-analysis of 59 clinical studies showed a significant correlation between thiazide-induced potassium depletion and increased blood glucose levels, as well as a correlation between potassium supplementation (or concomitant use of potassium-sparing agents) and attenuation of hyperglycemia.[89] In addition, a secondary analysis of the Systolic Hypertension in the Elderly Program (SHEP) investigated the relationship between serum potassium and thiazide-induced diabetes.[90] The risk for developing diabetes was increased in the first year of thiazide treatment.[90] In addition, independent of drug treatment, each 0.5-mEq/L decrease in serum potassium was associated with a 45% increased risk for development of diabetes throughout the course of the study.[90] A retrospective analysis of an extended follow-up of the SHEP trial was recently reported.[91] After a mean follow-up period of 14.3 years, patients treated with thiazide were more likely to develop new-onset diabetes. However, new-onset diabetes that developed in patients treated with thiazide diuretics was not associated with significantly increased cardiovascular or total mortality.

Alteration in fat distribution is another possible mechanism for thiazide-induced dysglycemia. Patients treated with 25 to 50 mg of thiazide daily had significant reductions in insulin sensitivity, compared with those treated with candesartan or placebo.[92] Serum potassium levels were significantly lower in patients taking thiazide, but levels in all groups remained within normal limits.[92] While taking thiazide, patients also developed a significantly higher hepatic fat content, and a significant correlation was found between hepatic fat content and decreased insulin sensitivity.[92] Whether decreased insulin sensitivity was a result of this visceral fat accumulation or vice versa is not clear. Low-grade inflammation assessed with C-reactive protein was also significantly increased with thiazide treatment,[92] suggesting a possible role for inflammation in the development of insulin resistance. Of clinical interest is that patients with abdominal obesity are more likely to experience new-onset diabetes with thiazide treatment than those without abdominal obesity.[93,94] In older studies of thiazide diuretics, the dosage (or equivalent in vitro concentration) used was 50 mg of thiazide or more. Today, clinicians do not often prescribe doses greater than 25 mg of thiazide or its equivalent. Of note, findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) diabetes extension study suggest that thiazide-related incident diabetes has less adverse long-term CVD impact than incident diabetes that develops while patients are taking amlopidine or lisinopril.[95]

Calcium Channel Blockers

In 16,176 hypertensive patients with CAD enrolled in the International Verapamil SR Trandolapril Study (INVEST), a verapamil-based treatment regimen was associated with a decrease in the incidence of type 2 diabetes from 8.2% to 7.0% compared with an atenolol-based regimen.[96] Diabetes incidence was not a predefined endpoint in this study, and no adjustment was made for concomitant therapies, which could potentially affect diabetes incidence. In ALLHAT, the risk of incident diabetes at 4 years of follow-up was 9.3% with the calcium channel blocker amlodipine and 7.8% with the ACE inhibitor lisinopril.[97]

High-dose calcium channel blocker therapy can inhibit insulin release, but this effect is generally not seen with usual therapeutic doses.[98,99] Impaired insulin release appears to be counterbalanced by increased peripheral glucose uptake, such that the predominant effect of these agents is metabolically neutral or favorable.[98,100] Evidence from animal models suggests that vasodilation and improved peripheral blood flow may explain the potential improvement in insulin sensitivity seen with calcium channel blockade.[101] Thus, calcium channel blockers appear to have a neutral or slightly favorable effect on glucose metabolism.

Niacin

Niacin is known to increase insulin resistance and have adverse effects on blood glucose levels, but to have favorable effects on plasma lipids and lipoproteins. Niacin reduces plasma triglycerides, increases HDL-C, and reduces LDL-C modestly. Concerns have been raised about use of niacin in diabetic patients because of its adverse effects on insulin resistance and blood glucose levels.[102,103]

Reports from the Assessment of Diabetes Control and Evaluation of the Efficacy Niaspan Trial (ADVENT),[104] the Arterial Disease Multiple Intervention Trial (ADMIT),[105] and the HDL-Atherosclerosis Treatment Study (HATS)[106] have shown that the modest increase in glucose level caused by niacin treatment could be easily counteracted by adjusting the diet, amount of exercise, and dose of glucose-lowering medication. During the follow-up period in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, the dose of the study drug was reduced in 6.3% of the patients in the niacin group and 3.4% of the patients in the placebo group ($P < 0.001$). Increased glucose level was the primary reason for dose reduction in 5 (0.3%) and 10 (0.6%) patients (placebo versus niacin, respectively). The study drug was discontinued in 25.4% of the patients in the niacin group and in 20.1% of the patients in the placebo group ($P < 0.001$). The primary reason for discontinuation because of increased glucose level was reported in 14 (0.8%) and 29 (1.7%) patients (placebo versus niacin, respectively).[107] During HATS, there was a 20% rise in insulin levels in the groups taking niacin. This finding was accompanied by a 2% to 3% increase in fasting glucose levels. In patients with diabetes,[106] glucose levels increased by approximately 15% by 3 months in those receiving niacin, but returned to baseline by 8 months. Changes in glucose-lowering medications were permitted, but no data were provided. Glycemic control among patients with diabetes returned to pretreatment values after 8 months, probably because of better diabetes management.[106] The changes in blood glucose with extended-release (ER) niacin are typically modest and transient and more prevalent in patients with diabetes.[104,105] On average, the rise in HbA1c levels is small and can be managed by titrating hypoglycemic therapy, but blood glucose levels should be closely monitored in patients with difficult-to-treat diabetes.

The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, a large randomized trial that comprising 25,673 patients tested the use of extended-release niacin and the antiflushing agent laropiprant for the reduction of major vascular events, did not find a significantly reduced risk of major vascular events in patients with well-controlled LDL-C levels. The failure of niacin in the HPS2-THRIVE study was first announced in late December 2012. In light of these findings, the role of extended-release niacin for the prevention of CVD should be reconsidered, given the side effects of niacin including a 25% increased risk of new-onset diabetes and the difficulties in controlling glucose level when patients are taking niacin.[108]

Statins

Statin therapy, particularly high-dose therapy, is associated with increased diabetes risk.[109,110] These study observations are supported by results from two meta-analyses including over 100,000 participants demonstrating that long-term statin intake was associated with increased risk of new-onset diabetes.[111,112] Several meta-analyses have been conducted to elucidate the effect of statins on glucose metabolism.[111,113,114] Treatment with statins has been associated with a 9% increase in the risk of developing diabetes without any clear differential effect among individual statins.[111,113] However, the overall data available strongly suggest that the reduction in CVD events outweighs the minor effect on glucose homeostasis.[115,116] In contrast, it has been suggested that various statins may affect glucose metabolism differentially.[114,117]

Pravastatin appeared to improve insulin sensitivity, whereas simvastatin was associated with an adverse effect on glucose metabolism.[114] Also, atorvastatin and rosuvastatin nonsignificantly worsened insulin sensitivity.[114] Rosuvastatin administration in hypercholesterolemic patients with impaired fasting glucose was associated with a dose-dependent increase in insulin resistance.[118,119]

The mechanisms by which statins may impair glucose metabolism are not fully understood. Several mechanisms may be responsible for these diabetogenic effects (**Box 6-4**).[120] One possibility is a statin-mediated decrease in various metabolic products of the mevalonate pathway, such as the isoprenoids farnesyl pyrophosphate or geranylgeranyl pyrophosphate. These isoprenoid molecules have been linked with the upregulation of the membrane transport protein glucose transporter 4 (GLUT-4) in 3 T3-L1 adipocytes, thus augmenting glucose uptake.[121] In type 2 diabetic mice and human patients treated for 3 months, atorvastatin impaired glucose tolerance and GLUT-4 expression by inhibiting isoprenoid biosynthesis.[122] In addition, a possible role for the small guanosine triphosphate (GTP) binding proteins as regulators of glucose-mediated insulin secretion by beta cells has been suggested.[123] Statins, by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, decrease the production of these substances. High doses of lipophilic statins decreased insulin secretion from beta cell lines, mediated either by the inhibition of HMG-CoA reductase or direct cytotoxicity.[124] Therefore the lipophilicity of individual statins may influence their effects on glucose metabolism. Statins, particularly the lipophilic compounds, have been shown to inhibit glucose-induced cytosolic Ca^{2+} elevations and insulin secretion as a result of blockade of L-type Ca^{2+} channels in rat islet beta cells.[125] Simvastatin attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients at risk of the metabolic syndrome.[126] However, this opposes the observed effects of rosuvastatin, which is known to be a hydrophilic molecule. A protective effect of pravastatin,

BOX 6-4 Potential Mechanisms by Which Statins May Impair Glucose Metabolism

Decrement in various metabolic products of the mevalonate pathway
- ↓ Isoprenoid farnesyl pyrophosphate
- ↓ Geranylgeranyl pyrophosphate

↓ Glucose transporter 4 expression

↓ Protein isoprenylation and affect on the distribution of several small G proteins
- ↓ Potentiation of nutrient-induced insulin secretion by bombesin and vasopressin

↓ Insulin secretion from beta cell lines
- Blockade of L-type Ca^{2+} channels in animal models

which is a hydrophilic statin, on progression to diabetes has been reported in a post hoc analysis of West of Scotland Coronary Prevention Study (WOSCOPS).[117]

Ezetimibe and Bile Acid Sequestrants

Studies have suggested that treatment with ezetimibe may be associated with beneficial effects on glucose metabolism.[127–129]

Bile acid sequestrants are therapeutic adjuncts to statins for lowering LDL-C. In patients with type 2 diabetes, they also reduce fasting blood glucose and glycated hemoglobin.[130–138] Similar studies have been performed in patients with prediabetes and showed reductions in fasting plasma glucose[139] and glycated hemoglobin levels.[140,141] In another study, colesevelam produced a small but statistically significant reduction in fasting glucose levels but no significant changes in level of glycated hemoglobin.[142] However, colesevelam therapy neither reduced the nonesterified fatty acid levels nor reduced the fasting or postprandial insulin levels.[142] Thus the effect on fasting glucose is probably unrelated to the changes in insulin resistance or fatty acid oxidation. Nevertheless, the add-on effect of colesevelam regarding glycated hemoglobin may be clinically relevant in patients with type 2 diabetes, with colesevelam having a product indication for treatment of type 2 diabetes.[143]

Fibrates

In a post hoc analysis of 303 patients with impaired glucose tolerance from the Bezafibrate Infarction Prevention (BIP) trial, bezafibrate therapy was associated with a reduction in diabetes incidence from 54% to 42% compared with placebo (hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.49-0.99).[144] It was shown that the administration of PPAR-α agonist fenofibrate for 3 months did not significantly affect insulin sensitivity or resistin and adiponectin concentrations in obese patients with type 2 diabetes mellitus. The lack of insulin-sensitizing effects of fenofibrate in humans relative to rodents could be a result of a generally lower PPAR-α level in humans relative to rodents.[145,146] However, bezafibrate, in comparison with other fibrates, has a unique characteristic profile of action because it activates all three PPAR subtypes (α, γ, and δ) at comparable doses.[147,148]

Cholesteryl Ester Transfer Protein

HDL-C particles may have antidiabetic properties. There is in vitro evidence that HDL-C enhances the uptake of glucose by skeletal muscle[149] and stimulates the synthesis and secretion of insulin from pancreatic beta cells.[150] The elevation of HDL-C accompanying genetic cholesteryl ester transfer protein (CETP) deficiency is associated with decreased levels of plasma glucose. The experimental CETP antagonist torcetrapib lowered both glucose and insulin levels in patients without diabetes, although the effects were not as great in patients with diabetes[151]; the clinical development of this compound was halted because of excess mortality observed in the large cardiovascular outcomes trial, Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial.[152] This discovery was not expected because it is known that torcetrapib increased plasma levels of aldosterone,[152] an effect that would be predicted to worsen rather than improve glucose control,[153] because spironolactone has beneficial effects in attenuating chlorthalidone-induced insulin resistance in humans, independent of blood pressure reduction.[154] Attention has recently been focused on the relationship between aldosterone and impairment of glucose metabolism.[155]

Digoxin

Human studies report in vitro observations of the inhibitory effect of digoxin on epinephrine-induced lipolysis.[156] These results confirm a previous report by Ogilvie and Klassen[157] that digoxin stimulates glucose uptake in human skeletal muscle. Thus, even if perfusion of forearms with digoxin markedly inhibited epinephrine-induced lipolysis, the metabolic effects of digoxin administration on cardiac myocytes or whole body glucose metabolism require further investigation. It is plausible that digoxin can directly alter the energy supply of cardiac muscle as well as indirectly decrease circulating free fatty acids in clinical states.

NONCARDIOVASCULAR PHARMACOLOGIC TREATMENT THAT INFLUENCES GLUCOSE METABOLISM AND THE DEVELOPMENT OF DIABETES

Thiazolidinediones

Rosiglitazone

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial reported that 3 years of therapy with rosiglitazone compared with placebo reduced the primary outcome of diabetes or death by 60%.[158] It showed that during the active treatment phase, rosiglitazone reduced diabetes alone by 62% and increased the likelihood of regression to normoglycaemia by 83%. Other analyses also showed that rosiglitazone improved beta cell function.[159] However, time-limited exposure to rosiglitazone reduces the longer-term incidence of diabetes by delaying but not reversing the underlying disease process.[160] The DREAM On passive extension follow-up study was conducted at a subset of 49 clinical sites located in nine countries. Findings strongly suggest that rosiglitazone slows the progression of beta cell dysfunction while it is being taken and that the process resumes at the control rate once the drug is stopped.[160] However, the clinical relevance of these observations is limited because of the restricted use of rosiglitazone based on signals of increased myocardial infarction risk with the drug.

Ethnicity is an important risk factor for type 2 diabetes in dysglycemic individuals. All ethnic groups experienced a large significant reduction in diabetes risk because of rosiglitazone. Of note, the magnitude of this reduction differed by ethnicity. South Asians showed a higher hazard for the primary outcome compared with Europeans adjusted for age, sex, BMI, waist-to-hip ratio, and geographic region. A lesser increment in risk was seen in black trial participants. A significant reduction in risk of the primary outcome with rosiglitazone treatment assignment was seen in all ethnic groups, but the treatment effect significantly differed by ethnicity, with South Asians experiencing a smaller and Latinos a larger preventive effect.[161]

Pioglitazone

The Actos Now for the Prevention of Diabetes (ACT NOW) study examined the effect of pioglitazone on diabetes risk and cardiovascular risk factors in adults with impaired glucose tolerance. As compared with placebo, pioglitazone

reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus but at the cost of significant weight gain (mean weight gain was 3.6 kg). Pioglitazone reduced the risk of conversion to diabetes in patients with isolated impaired glucose tolerance, in those with both impaired fasting glucose and impaired glucose tolerance, in both men and women, and in all age and weight groups.[162]

Metformin

In the Diabetes Prevention Program (DPP), people with impaired glucose tolerance were randomly allocated to a lifestyle intervention, metformin, or placebo. The DPP demonstrated that metformin or lifestyle modification could prevent or delay the development of diabetes in individuals with impaired fasting glucose and impaired glucose tolerance. In the 2.8-year follow-up of the DPP,[163] the incidence of diabetes was 58% lower in the lifestyle intervention versus 31% lower in the metformin versus the placebo group. The average weight loss was 5.6, 2.1, and 0.1 kg in the lifestyle intervention, metformin, and placebo groups, respectively. Subsequently, all participants were offered a modified lifestyle intervention, and those who had been allocated to metformin were provided with open-label metformin. Participants allocated to the lifestyle group achieved a 34% reduction in diabetes versus placebo over the full 10-year follow-up period, and those allocated to metformin (of whom 70% continued to take metformin) achieved an 18% reduction.[164] During the 10-year follow-up,[164] the original lifestyle group partly regained weight that had been lost, whereas weight loss with metformin was maintained. In the DPP, intensive lifestyle interventions were superior to metformin in the prevention of incident type 2 diabetes.

The DPP did not observe a sex-race influence on the effects of metformin.[165] Two economic analyses of the DPP study have been performed.[166,167] In a cost-effectiveness analysis from a societal perspective, the metformin intervention cost $31,300 per case of diabetes delayed or prevented and $99,600 per quality-adjusted life-year gained over the 3-year duration of the study. Assuming the use of lower-priced generic metformin, cost estimates decreased to $14,300 and $35,000, respectively. In all analyses, the lifestyle intervention was more economically attractive than metformin. A second economic analysis, performed in Europe, documented that metformin was cost-saving in four of the five European countries studied.[168]

Metformin is a promising medication for the prevention or reduction of the incidence of gestational diabetes mellitus and preeclampsia in women with polycystic ovary syndrome.[169] Use of metformin as an insulin-sensitizing drug in pregnant women with polycystic ovary syndrome is quite well established.[170–172] Metformin significantly reduces the incidence of early pregnancy loss by its beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to first-trimester spontaneous abortion in patients with polycystic ovary syndrome.[173–176] It has been reported that metformin is not teratogenic and does not have a negative impact on fetal outcome, although metformin is classified as a pregnancy class B drug.[177]

It has been postulated that postreceptor effects of metformin include suppression of hepatic glucose output, increased insulin-mediated glucose use in peripheral tissues (such as muscle and liver), and an antilipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis. Its pharmacologic mechanisms of action are different from those of other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and use.[170] The most common side effects associated with metformin are gastrointestinal in nature: abdominal pain, distention, diarrhea, dyspepsia, taste disturbance, and flatulence.

Acarbose

The effect of acarbose on incident type 2 diabetes was studied in a randomized clinical trial and in a cohort study.[178,179] In the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), the incidence of diabetes was 32% in the acarbose versus 42% in the placebo group during 39 months of observation.[179] Almost 25% of individuals discontinued therapy early, predominantly because of acarbose-induced gastrointestinal side effects. At the study's end, 60% of eligible patients were observed for a 3-month washout period, during which 15% of acarbose-treated patients developed diabetes compared with 10.5% of placebo-treated patients. In a secondary post hoc analysis including data from a long-term passive follow-up of the trial cohort, acarbose significantly reduced cardiovascular events from 4.7% to 2.1%.[180]

Antiobesity Agents

Orlistat induces weight loss by inhibition of intestinal absorption of dietary fats. Whereas orlistat significantly reduced the incidence of type 2 diabetes from 9% to 6% and reduced weight by 2.8 kg compared with placebo in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, the attrition rate was 57%.[181] Ninety-one percent of orlistat-treated patients experienced gastrointestinal side effects in the first year of therapy compared with 65% of the placebo arm. A pooled analysis of randomized clinical trials enrolling 642 obese patients reported a nonsignificant reduction in the incidence of type 2 diabetes from 2% to 0.6% with orlistat therapy.[182] The 95% CIs were wide, reflecting the small sample size and low absolute incidence of diabetes within these trials, associated with attrition rates averaging 30%.

The potential exists for some blood pressure–lowering medications to influence body weight, and concern in this regard has focused primarily on beta blockers and their potential to promote weight gain or to hinder weight loss.[183] One study examined the interaction between sibutramine and blood pressure lowering on weight loss and metabolic parameters. Two different blood pressure–lowering strategies were studied: (1) conventional therapy involving combinations of beta-blocker and thiazide diuretic treatment and (2) blood pressure–lowering therapy with two different calcium channel blocker–ACE inhibitor–based treatments. Blood pressure–lowering efficacy was similar between these two treatment strategies, but sibutramine-induced weight loss was markedly attenuated in the beta-blocker–thiazide–treated patients. Moreover, the sibutramine-induced improvements in glucose tolerance also were markedly attenuated by the beta-blocker–thiazide diuretic treatment.[184] These findings are important because they support the perception

that beta blocker–based treatments in particular may promote weight gain[183] and that beta blocker–thiazide–based treatments enhance the risk of development of diabetes.[185,186]

Antipsychotic Medication

Metabolic as well as cardiovascular comorbidities are increasingly important in mental disorders.[187,188] Patients with schizophrenia have an excess mortality, two or three times as high as that in the general population. This mortality gap translates into a 13- to 30-year shortened life expectancy.[189–191] It is increasingly recognized that most antipsychotic agents are closely linked with adverse effects on weight, lipids, glucose metabolism, and CVD. In 2003, the U.S. Food and Drug Administration (FDA) required that class warnings be added to the labeling of atypical or second-generation antipsychotic drugs, documenting the increased risk of dysglycemia and diabetes, and mandating that all drug manufacturers mail health-care professionals about this labeling change.[192]

Despite the increased cardiometabolic risk profile in individuals with mental illness who take antipsychotic medication, metabolic screening practices are often incomplete or inconsistent. In routine clinical practice, the frequency of metabolic monitoring is low in people prescribed antipsychotic medication. Although guidelines can strongly suggest to increase monitoring, most patients still do not receive adequate testing. Using data pooled from five countries involving 218,940 patients at baseline and 71,594 after publication of guidelines endorsing systematic metabolic surveillance of patients with mental disorders, it was found that metabolic monitoring rates were generally low and were not materially influenced by the guideline publication.[193]

Regarding diabetes, in studies from the United States, 37.3% of patients with mental illness underwent plasma glucose testing as part of routine (preguideline) care. In the United Kingdom the equivalent proportion was 41.6%. Nineteen studies reported on glucose monitoring according to medical chart, with a rate of 48.7% versus 33.5% in database studies. For inpatients, 44.0% underwent glucose tests as part of routine care compared with 46.2% among outpatients.[192] Effective monitoring of metabolic disturbances is not sufficient on its own, as appropriate treatment should follow. However, patients with psychiatric diagnoses often seem to receive an inferior quality of care in several medical areas,[194] including metabolic and diabetes care.[195–198] In the largest controlled study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), approximately one third of patients met National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) criteria[199] for metabolic syndrome at baseline, whereas 88% of patients with dyslipidemia were untreated, as were 62% with hypertension and 38% with diabetes.[200,201]

Erythromycin

Erythromycin mimics the effect of the gastrointestinal hormone motilin by binding to its receptor and acting as a motilin agonist. Motilin stimulates insulin secretion at lower doses than are required to stimulate gastric contractile activity. Because there are no motilin receptors in the pancreas,[202] the actions of motilin and motilide-like molecules on insulin secretion are most likely to be mediated by vagal-cholinergic muscarinic pathways linked to serotonergic receptors, a common mechanism in the stimulatory effect of motilin on muscle contraction in the stomach and on pancreatic polypeptide secretion from the endocrine pancreas.[202–204] Erythromycin seems to be able to stimulate glucose-dependent as well as vagally mediated insulin secretion, common defects encountered in patients with type 2 diabetes. Erythromycin given orally has an antidiabetogenic effect, and therefore erythromycin derivatives that lack the antibacterial activity could be of therapeutic value in patients with type 2 diabetes.[205] Erythromycin given orally for 1 or 4 weeks improves glycemic control in patients with type 2 diabetes, at lower doses (600 to 1200 mg/day) than those used for the antibacterial activity of the compound. Erythromycin enhances insulin release, both basal and glucose stimulated.[205] Also, erythromycin accelerates delayed gastric emptying associated with various medical conditions such as diabetes mellitus, cancer therapy, postvagotomy conditions, and progressive systemic sclerosis.[202,206]

Human Immunodeficiency Virus Treatment

Type 2 diabetes is a growing concern in the human immunodeficiency virus (HIV)–infected population. The successful introduction of combination antiretroviral therapy to treat HIV infection with prolonged life expectancy has led to the emergence of several chronic conditions, including diabetes and CVD. In HIV-infected patients, the presence of concomitant diabetes is associated with a 2.3-fold to 2.4-fold higher rate of myocardial infarction than in those without diabetes,[207] and a 2.4-fold higher rate of CAD.[208] The mechanism underlying the increased risk of diabetes in HIV-infected patients is multifactorial.[209,210] HIV-specific influences may play a role, including chronic inflammation and antiretroviral therapy–related factors such as the interference of specific protease and nucleoside reverse transcriptase inhibitors with glucose and lipid metabolism, subcutaneous fat losses, and increased abdominal adiposity.[211,212] Among HIV-infected patients, the dominant risk factors for patients with diabetes generally mirror those of the general population: older age, higher BMI, lower HDL-C, higher triglycerides, minority race or black or Asian ethnicity, and male sex. Previous reports have described that the exposure to protease and also nucleoside reverse transcriptase or non-nucleoside reverse transcriptase inhibitors[213–215] differentially affects the prevalence and the incidence of diabetes.

Estrogen

Studies have investigated associations between estrogen use and diabetes incidence. Post hoc analysis of the Heart and Estrogen/Progestin Replacement Study (HERS) reported that combination estrogen and progesterone therapy was associated with a significant reduction in the incidence of diabetes from 9.5% to 6.2% versus placebo.[216] The Nurses' Health Study found that over 12 years, current estrogen use was associated with a significantly lower diabetes incidence compared with patients who had never used estrogen.[217] Of other cohort studies,[218–221] only one reported a significant covariate-adjusted reduction in diabetes incidence in users of estrogen replacement therapy compared with nonusers. It is important to emphasize that several trials failed to adjust for potentially important covariates such as family history, weight, or baseline glucose measurements.

Antineoplasic Agents

Potential factors triggering hyperglycemia with cancer and/or antineoplasic regimens include direct infiltration of the pancreas by leukemic cells, beta cell dysfunction induced by chemotherapeutic agents such as L-asparaginase, and increased insulin resistance and hepatic gluconeogenesis secondary to glucocorticoids. Most patients have a transient form of medication-induced diabetes that appears to resolve after discontinuation or tapering down of the therapy, such as glucocorticoids. As patients receive organ, bone marrow, and stem cell transplants, rates of medication-induced diabetes may be on the rise, paralleling increasing rates of obesity and type 2 diabetes.[222–224] Therapies commonly implicated in medication-induced diabetes (glucocorticoids, tacrolimus, L-asparaginase, cyclosporine) are often used in organ transplant recipients.

INVASIVE TREATMENT TO PREVENT OR REVERSE DIABETES

Bariatric Surgery

Major, durable weight loss is uncommon with medical and/or behavioral approaches, and adequate glycemic control often remains elusive.[225] Clinicians note that bariatric operations can dramatically resolve type 2 diabetes, often long before and out of proportion to postoperative weight loss. Indeed, bariatric operations, especially intestinal-bypass variants, exert powerful antidiabetes effects.[226,227] Nowadays, five bariatric surgical procedures are considered acceptable therapy for appropriate patients: roux-en-Y gastric bypass (RYGB); laparoscopic adjustable gastric banding (LAGB); laparoscopic sleeve gastrectomy (LSG); biliopancreatic diversion (BPD); and BPD with duodenal switch. Weight loss after RYGB, LAGB, and LSG procedures is primarily caused by a decrease in energy intake because there is little or no malabsorption after these procedures, and weight loss after BPD with or without duodenal switch is a result of a combination of decreased energy intake and nutrient malabsorption.

The therapeutic superiority of bariatric surgery over medical therapy has been shown in three 1-year or 2-year prospective randomized controlled trials.[228–230] In one study, 73% of patients who underwent LAGB surgery in contrast to only 13% in the medical-lifestyle therapy group achieved remission of type 2 diabetes.[228] In the second study, 42% of patients who underwent RYGB surgery and 37% who underwent LSG but only 12% treated with intensive medical therapy achieved remission of diabetes.[229] Finally, in the third study, 95% of patients who underwent BPD and 75% of those who underwent RYGB surgery (with the same weight loss) but no patients randomized to conventional medical therapy achieved remission of type 2 diabetes.[230]

Short- to moderate-term diabetes remission rates have been reported to be 80% to 85% after RYGB and even higher after BPD.[231] Two randomized controlled trials comparing bariatric surgery procedures with medical therapy to treat type 2 diabetes for 1 to 2 years, including patients below the usual BMI threshold for surgery (BMI <35 kg/m^2 with comorbidities or <40 kg/m^2 without comorbidities), revealed that surgery yielded better glycemic control, diabetes remission, and reduction of other cardiovascular risk factors, with seemingly acceptable rates of complications.[229,230] Mingrone and colleagues[230] examined RYGB and BPD, whereas Schauer and colleagues[229] studied RYGB and sleeve gastrectomy, all of which were compared with medical-lifestyle therapy in patients with type 2 diabetes. Both studies showed better results after surgery with regard to diabetes remission, improved glycemic control, and reductions in cardiovascular risk factors such as dyslipidemia and hypertension. In the first trial, postsurgical diabetes remission rates were spectacular: 75% after RYGB, 95% after BPD, and 0% with medical-lifestyle therapy alone.[230] Results seemed less striking in the second study: 42%, 37%, and 12% diabetes control after RYGB, sleeve gastrectomy, and medical-lifestyle therapy, respectively.[229] This between-trial heterogeneity is probably a result of differences in the primary endpoint, which in the study by Mingrone and colleagues was a glycated hemoglobin (HbA1c) value below 6.5% in patients off all diabetes medications, as opposed to 6.0% or lower (with or without medications) in the study by Schauer and colleagues. Whereas fewer patients achieved the latter study's more stringent endpoint, the HbA1c decrement after surgical procedures was noteworthy (from approximately 9.4% to approximately 6.5%), with an important decrease in glucose-lowering medication.

Specific characteristics have been identified that predict the response of type 2 diabetes to surgery-induced weight loss among patients undergoing RYGB surgery. Several factors have been associated with treatment failure: longer duration of type 2 diabetes, inadequate postoperative weight loss, more severe diabetes requiring insulin therapy before surgery, and older age. Of importance, early remission does not necessarily translate into long-term success, and relapse can occur. Data from the Swedish Obese Subjects (SOS) long-term observational study, which evaluated the effect of bariatric surgery in 4047 patients with type 2 diabetes, found that one half of the 72% of patients who had achieved diabetes remission at 2 years after surgery remained in remission at 10 years.[232] The precise reasons for recurrence of diabetes are not known but are likely related to recidivism of weight loss because relapse or worsening of type 2 diabetes is associated with weight regain.

An important confounding factor in interpreting the efficacy of bariatric surgery in the management of type 2 diabetes is the absence of a uniform definition of diabetes "remission" or "resolution," and different criteria have been used in different studies. Remission has most often been defined as the withdrawal of all diabetes medications, in conjunction with normal fasting plasma glucose levels (ranging from <100 to <126 mg/dL) and/or a normal HbA1c level (ranging from $<6\%$ to $<7\%$).[227] Obviously, differences in the definition of remission among studies will lead to differences in estimated remission rates. Nevertheless, the type 2 diabetes remission rate is not the same with all bariatric surgical procedures. Results from a meta-analysis involving approximately 8000 patients with type 2 diabetes found that the rate of diabetes resolution was much greater in patients who underwent surgical procedures that involved anatomic diversion of the upper gastrointestinal tract (BPD and RYGB: 95% and 80% resolution rates, respectively) than in procedures that implied a restrictive approach (LAGB: 57% resolution rate).[231,233]

Medical costs for a patient with type 2 diabetes are greater than costs for a patient without diabetes. Estimated yearly costs of managing a patient with diabetes in the United States

($13,243) are more than five times that of a patient without diabetes ($2560).[234] The largest components of costs are hospital inpatient care (50%), medication and supplies (12%), retail prescriptions to treat complications (11%), and physician office visits (9%).[234] Advantages of bariatric surgery with regard to diabetes translate into considerable economic benefits. Surgery costs for laparoscopic surgery may fully be recovered after 26 months. These data suggest that surgical therapy is clinically more effective and ultimately less expensive than standard therapy for diabetes patients with BMI of 35 kg/m^2 or higher.[235] This has also been reported in Canada, where health care system coverage differs from the United States. The initial costs of surgery can be amortized over 3.5 years.[236]

Observed metabolic effects following some procedures implicate weight-independent antidiabetes mechanisms.[226,227] These benefits result in part from mechanisms beyond reduced food intake and body weight because glycemic improvements precede substantial weight loss. Mingrone and colleagues[230] found that all the surgical patients achieved glycemic control without diabetes medications within only 15 days after surgery. Schauer and colleagues[229] reported that diabetes medication use decreased postoperatively, long before maximum weight loss occurred. Recent studies corroborate a growing body of evidence showing that weight-independent mechanisms contribute to diabetes remission after some bariatric procedures.[227,237] This notion is based primarily on (1) the early postoperative effects of RYGB surgery on glycemic control, (2) the long-term efficacy of different surgical procedures on resolution of type 2 diabetes, (3) the effect of duodenojejunal bypass (DJB) surgery, which bypasses the upper gastrointestinal tract but causes minimal weight loss, (4) the hormonal response to glucose or mixed-meal ingestion, and (5) upper gastrointestinal tract bypass in rodent models. Operations that reroute chyme in such a way that the duodenum and proximal jejunum are bypassed, resulting in chyme delivery directly to the jejunum, may be a promising pathophysiologic avenue in diabetes management.

Nonsurgical Duodenal Exclusion

An alternative approach would be to duplicate the effects of the gastric bypass or BPD procedure by diverting chyme from the proximal small intestine. The duodenojejunal bypass liner (DJBL) is an endoscopically placed and removable intestinal liner developed to achieve duodenal exclusion and promoting significant weight loss beyond a minimal sham. The DJBL is a 60-cm impermeable fluoropolymer device, which, after endoscopic deployment in the proximal duodenum, functions to prevent partially digested food from contacting the proximal intestine, similar to RYGB but without gastric restriction. Bile and pancreatic secretions pass along the outer wall of the liner and mix with the chyme exiting distal to the liner into the jejunum. Mean weight loss averages approximately 10 kg after 12 weeks with diabetes remission in several patients.[238–240] There seems to be a procedural learning curve of five to seven procedures.[240] Most DJBL-related adverse events are mild or moderate in the implantation patients. Many of the adverse events occurring within the first 2 weeks likely reflect adaptation to the DJBL. Mild bleeding is an expected adverse event associated with the anchoring of the device in the gastric pylorus.

SUMMARY

Regarding cardiovascular medications, although not definitive, the available evidence from bench research and clinical studies suggests a potentially beneficial effect on diabetes incidence for inhibitors of the RAAS system, a neutral effect for calcium channel blockers, and a detrimental effect for thiazide diuretics, nonvasodilating beta blockers, niacin, and statins. Vasodilating beta blockers have a number of favorable glycometabolic effects, although their effect in incident diabetes has not been fully explored.

Potentially diabetogenic agents should not be denied to patients with compelling indications for these drugs because of concerns that blood glucose levels will increase. Indeed, beta blockers have been well proven to lower cardiovascular morbidity and mortality in post–myocardial infarction and in chronic systolic heart failure patients. They should be considered among first-line agents in such patient populations. In patients with diabetes and nephropathy, ACE inhibitors or ARBs are considered to be first-line therapy. In patients without nephropathy, ACE inhibitors were associated with a reduction in cardiovascular morbidity and mortality in patients with diabetes. Because hypertensive patients with impaired fasting glucose or impaired glucose tolerance are commonly obese with several comorbidities, many will require multidrug antihypertensive therapy. Therefore, the choice of initial agent is not as important as ensuring that blood pressure treatment goals are achieved. The diabetogenic potential of thiazide diuretics and nonvasodilating beta blockers can be minimized by using the lowest effective dose possible. In addition, minimizing hypokalemia with thiazides and using alpha$_1$-adrenergic receptor–selective agents or agents with concomitant beta$_2$-blocking activity will also limit the detrimental effects of thiazides and beta blockers on blood glucose levels. The European Society of Hypertension and European Society of Cardiology guidelines note that, compared with nonvasodilating beta blockers, vasodilating beta blockers have fewer or no dysmetabolic effects and are less likely to cause new-onset diabetes.[241] In addition, the American Association of Clinical Endocrinologists guidelines state that third-generation beta blockers (carvedilol and nebivolol) induce vasodilation and increase insulin sensitivity and, as a result, are particularly appropriate for the treatment of patients with diabetes.[242] Management of dyslipidemia is also very important in patient with diabetes. Statins should not be withheld on the basis of a potential, small risk of new-onset diabetes emerging during long-term therapy.

Several other large global trials have clearly shown that noncardiovascular drug therapies, including metformin, acarbose, and glitazones, can also reduce the incidence of diabetes. Some of these trials also reported a significant increase in the probability of regression of dysglycemia to normoglycemia. All of the completed diabetes prevention trials studied individuals during a period of 3 to 4 years, after which formal application of the intervention was stopped. However, because diabetes is a lifelong disease, whether the effect of a relatively short exposure to a diabetes prevention intervention is sustained is clearly clinically important.

Bariatric surgery with its substantial weight loss reduces the incidence of diabetes in overweight insulin-resistant patients and is associated with remission of diabetes in a large percentage of patients. Although bariatric surgery appears to be an effective means for preventing and/or

reversing type 2 diabetes, it cannot be considered a practical response to the worldwide epidemic of diabetes. In addition, bariatric surgery is associated with the potential for both immediate and long-term adverse metabolic consequences. In considering the usefulness of bariatric surgery, it is also important to recognize that long-term follow-up is required before a beneficial therapeutic effect can be assigned in patients with diabetes because of the potential for weight regain that has been observed after some surgical procedures.

Overall, the most important goal in the management of patients with type 2 diabetes should be the attainment of treatment targets according to guidelines and the institution of therapies that have been proven to reduce cardiovascular morbidity and mortality. One must keep in mind that most patients with diabetes are overweight or obese and will require more than one drug to achieve blood pressure targets and high doses of statins to achieve lipid targets. In these individuals, the choice of initial therapy is less important than ensuring that risk factors are treated in a timely and aggressive fashion. Management of obesity is also pivotal in patients with diabetes.

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PART II

DIABETES AND ATHEROSCLEROSIS

7 Epidemiology of Coronary and Peripheral Atherosclerosis in Diabetes

Wolfgang Koenig

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PREVALENCE OF IMPAIRED GLUCOSE METABOLISM IN PATIENTS WITH MANIFEST ATHEROSCLEROSIS

In patients with manifest coronary heart disease (CHD), based on the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, approximately 20% of men and 25% of women had previously diagnosed diabetes. Newly detected diabetes was present in another 15% of men and approximately 10% of women.[1] More detailed data on the prevalence of abnormal glucose regulation in patients with manifest CHD across Europe were collected in the Euro Heart Survey on Diabetes and the Heart.[2] This survey involved 110 centers in 25 countries, recruiting more than 4000 patients referred to a cardiologist because of suspected coronary artery disease (CAD), including acute coronary syndrome (ACS) patients and those with stable symptoms. Of these patients, 31% had manifest diabetes. In 1920 patients without known diabetes, an oral glucose tolerance test (OGTT) was performed. The prevalence of impaired glucose tolerance (IGT) in those with ACS was 36%, with an additional 22% having newly detected diabetes. The corresponding figures in those with stable CAD were 37% and 14%, respectively. In another study[3] from Spain, in 662 consecutive patients admitted to the hospital without a previous diagnosis of diabetes who were referred for coronary intervention in 2005 and 2006, the prevalence of diabetes was 45%. Analyses of more than 120,000 patients from randomized clinical trials in the late 1990s, at least 30% of them coming from the United States, revealed a prevalence of diabetes of 23% in women and 15% in men.[4] Yet this certainly represents an underestimation as a result of selection bias and, most commonly, absence of systematic screening for incident diabetes.

Impaired glucose homeostasis (IGH) is also prevalent in this population. IGH comprises impaired fasting glucose (IFG) and IGT. IFG has been defined as a fasting glucose range of 110 to 126 mg/dL, and fasting glucose tolerance is pathologic if it exceeds 140 mg/dL according to 2-hour glucose levels after oral intake of 75 g of glucose (OGTT). Prevalence of these two entities may vary in different populations and may also not be consistently present in the same individual.

In the previously mentioned study[3] from Spain in 662 consecutive patients without a previous diagnosis of diabetes who were referred for coronary intervention in 2005 and 2006, IGT was present in 24.5%, yet IFG was seen in only 1%. Thus again, more than two thirds of this population with manifest atherosclerotic disease had an abnormal glucose metabolism. In the LURIC study in patients with manifest CHD, approximately 20% of men and 15% of women showed an abnormal OGTT result. Putting these figures into perspective, approximately two thirds of patients with manifest cardiovascular disease (CVD) had impaired glucose metabolism, as results from the LURIC study have shown.[1]

Thus, impaired glucose metabolism including manifest type 2 diabetes, pathologic oral glucose tolerance, and

IFG are prevalent in patients with manifest atherosclerosis. In particular, manifest type 2 diabetes is at least twice as frequent in CHD patients compared with those free of CHD.

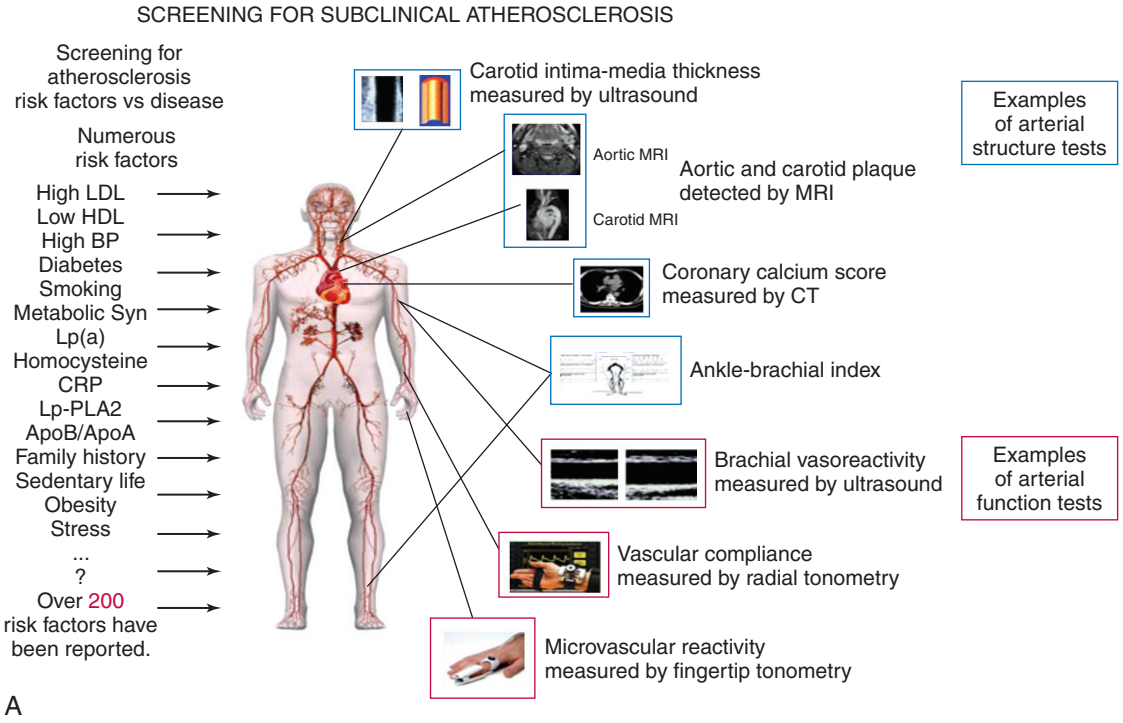
DIABETES MELLITUS AND SUBCLINICAL ATHEROSCLEROSIS

Subclinical atherosclerosis represents the early manifestation of vascular disease without clinical symptoms. It can be assessed in all three major vascular beds by noninvasive but also by invasive imaging techniques. For carotid atherosclerosis, measurement of the intima-media thickness (IMT) or the presence of plaque on high-resolution transcutaneous ultrasound represents the method of choice. In the coronary vascular bed, computed tomography (CT) seems promising, but more precise data can be gathered by several invasive techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT).[5] For the peripheral vascular bed, transcutaneous ultrasound and the ankle-brachial index (ABI) can be used (**Fig. 7-1**).[6] It has been well documented that the presence of subclinical atherosclerosis is associated with a higher incidence of clinical manifestations, yet in a number of studies the incremental value for risk prediction of these clinical manifestations (e.g., for IMT) above and beyond various risk scores such as the Framingham risk model did not yield clinically relevant results.[7] At present, evidence is accumulating that coronary calcium scoring by CT may be superior to various blood biomarkers and also may produce significant incremental value over and above risk scoring.[8] Epidemiologic data on the prevalence of subclinical coronary atherosclerosis and its association with incident CVD, as well as with all-cause mortality, have been published from several studies. One of the largest is the Cardiovascular Health Study (CHS), in which 1343 patients with diabetes, 1432 patients with IGT, and 2421 normoglycemic patients were identified by World Health Organization (WHO) criteria at the baseline examination in 1989-1990 and were followed on average for 6.4 years. Diabetic patients showed a higher prevalence of clinical and subclinical CVD at baseline, and the presence of subclinical disease was strongly related to CHD, stroke, and heart failure. This was particularly pronounced in diabetic patients, in whom the incidence of CHD and stroke was increased almost twofold in those presenting with subclinical disease versus those without (**Fig. 7-2**). A similar relative increase in all three endpoints, but on a lower level, was seen in patients with IGT.[9] Brohall and colleagues[10] published a systematic review of the relevance of carotid IMT in patients with type 2 diabetes mellitus and IGT and focused on the differences between IMT in diabetic patients with IGT versus controls. They included 23 studies with 20,111 patients. Among those were 4019 with diabetes and 1110 with IGT. In 20 of the 23 studies, diabetic patients showed an increased IMT compared with individuals in the reference group, whereas in patients with IGT, the increase in IMT was approximately one third of that observed in patients with diabetes. These findings suggest an older vascular age in diabetic patients of approximately 10 years, and further conclusions drawn from this review estimated an increased relative risk for myocardial infarction (MI) and stroke in the presence of diabetes of almost 40%.

Several studies have looked into carotid atherosclerosis in the setting of the metabolic syndrome. Prospective data from the Bruneck study[11] examined 888 patients aged 40 to 79 years, among whom 303 fulfilled the WHO criteria and 152 fulfilled the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) criteria for metabolic syndrome. Five-year changes in carotid status and its relation to incident fatal and nonfatal CHD were assessed. Patients with metabolic syndrome showed increased 5-year incidence and progression of carotid atherosclerosis, and also the incidence of clinical events was increased twofold compared with controls. This has recently been confirmed in the Multi-Ethnic Study of Atherosclerosis (MESA), in which individuals with metabolic syndrome or diabetes had a higher incidence and absolute progression of coronary artery calcification (CAC) compared with patients without diabetes. In addition, progression predicted future CHD events.[12]

Several studies also assessed the prevalence of CAC in various populations. Data from the Dallas Heart Study, a large population-based study in which the individual and joint associations among metabolic syndrome, diabetes, and atherosclerosis as defined by CAC were assessed, suggested that both metabolic syndrome and diabetes mellitus are independently associated with an increased prevalence of atherosclerosis, with the highest prevalence seen in those fulfilling both criteria.[13] In another study, by Wong and colleagues,[14] 1823 patients aged 23 to 79 years were screened for CAC. Of these patients, 279 had metabolic syndrome and 150 had diabetes mellitus. Prevalence of CAC clearly increased from the reference group to those with metabolic syndrome or diabetes, with 53.5%, 58.8%, and 75.3%, respectively, among men and 37.6%, 50.8%, and 52.6%, respectively, among women. CAC also increased with the number of components of the metabolic syndrome (0 to 5) from 34% to 58%. Risk assessment by the Framingham score estimated 41% of patients with metabolic syndrome as having a more than 20% per 10 years increased risk for CHD or a CAC greater than 75% for age and gender. Diabetic patients had a higher incidence and progression of CAC, and progression of CAC predicted clinical CHD events (**Fig. 7-3**). More recently, Elkeles and colleagues[15] prospectively evaluated CAC score as a predictor for cardiovascular events in type 2 diabetes based on 589 patients from the PREDICT study. Follow-up was 4 years, and first CHD and stroke events were identified as primary endpoints. The CAC score was found to be a highly significant independent predictor, with a doubling of calcium being associated with a 32% increase in risk of events—which only slightly decreased in multivariable analysis considering traditional risk factors, and even after adjustment for homocysteine, c-reactive protein (CRP), and the homeostasis model assessment (HOMA) index. The only variable that predicted primary endpoints independently of CAC scoring was the HOMA index. CAC scoring contributed significantly to improved discrimination over and above the Framingham CHD risk score as well as the United Kingdom Prospective Diabetes Study (UKPDS) CHD and CVD risk scores, with an increase in the area under the curve on average of 0.1 (0.63 to 0.73).

Thus, among various measures of subclinical disease, CAC scoring may represent the most promising tool to improve risk prediction in asymptomatic patients with type 2 diabetes mellitus.



A

COMPARISON AMONG ATHEROSCLEROSIS IMAGING MODALITIES

	Imaging targets	Resolution	Radiation	Invasiveness	Advantages and disadvantages
Coronary angiography	Coronary lumen	0.4 mm	Yes	Yes	Two-dimensional silhouette of lumen only, associated with cardiovascular events, accepted surrogate for expanded indication
IVUS	Coronary arterial wall	0.08–0.10 mm	No	Yes, catheter	Tomographic, volumetric assessment of changes in plaque burden and vascular remodeling with excellent resolution
Carotid ultrasound	cIMT and plaque	0.15 mm	No	No	Wide availability, wide clinical trial experience, low cost, technically demanding; further validation of 3D plaque assessment required
Coronary CT	Coronary lumen and wall	0.4 mm	Yes	No	Rapid acquisition, limited image resolution for plaque burden, radiation exposure
MRI	Carotid lumen and wall	0.5–1.0 mm	No	No	Plaque characterization possible, no validation with clinical events
PET	Metabolic activity in carotids and aorta	4 mm	Yes	No	Limited image resolution, limited ability to visualize coronary arteries, no validation with clinical events
OCT	Coronary arterial lumen and wall	Excellent, 0.01 mm	No	Yes, catheter	Best image resolution, limited depth of view Requires flushing of lumen
NIRS	Tissue spectral contrast (chemical assessment)	1 mm	No	Yes, catheter	Link to plaque status not clear, images difficult to interpret, limited spatial registration
NIR fluorescence	Exogenous molecular contrast	1 mm	No	Yes, catheter and injection of molecular compound	Limited depth of view due to blood absorption, may require flushing; high potential for molecular imaging; depends on targeted compound approval for humans

B

FIGURE 7-1 A, Screening for patients at risk for cardiovascular complications. **B,** Comparison of atherosclerosis imaging modalities. (***A*** *from Koenig W:* Circulation *116:3-5, 2007, reprinted from Naghavi M, Falk E, Hecht HS, et al: Vulnerable plaque to vulnerable patiet—Part III: Executive summary of the Screening for Heart Attach Prevention and Education (SHAPE) Task Force report.* Am J Cardiol *98(Suppl):2H-15H, 2006, with permission from Elsevier. Copyright 2006.* ***B*** *modified from Tardif JC, Lesage F, Harel F, et al: Imaging biomarkers in atherosclerosis trials,* Circ Cardiovasc Imaging *4:319-333, 2011.)*

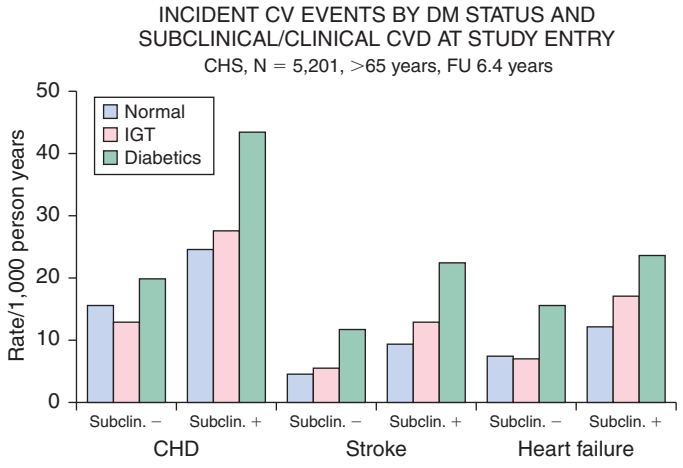
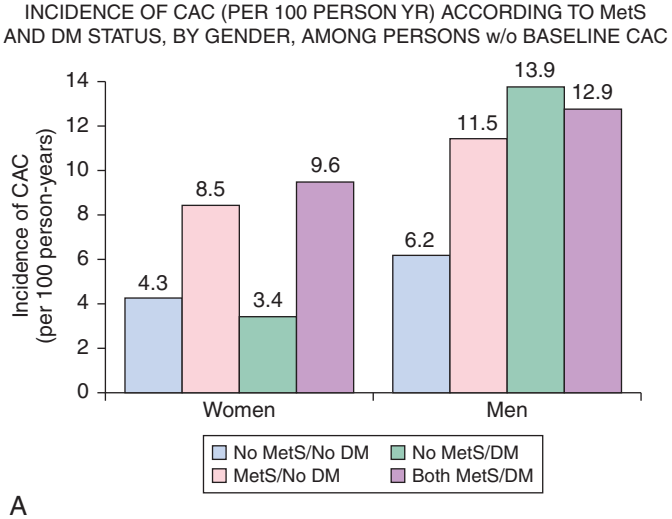


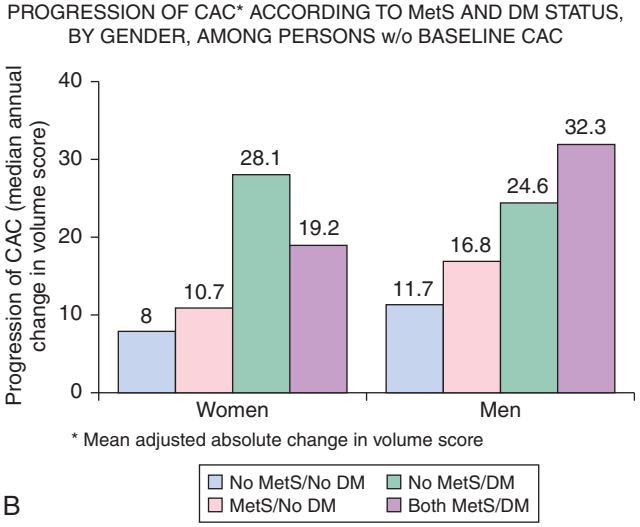
FIGURE 7-2 Diabetes status and presence of subclinical and clinical CVD at baseline and incidence of specific events among men and women in the CHS. DM = Diabetes mellitus. *(Modified from Kuller LH, Velentgas P, Barzilay J, et al: Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality,* Arterioscler Thromb Vasc Biol *20:823-829, 2000.)*

CLINICAL MANIFESTATIONS OF ATHEROSCLEROSIS IN PREDIABETES, METABOLIC SYNDROME, AND TYPE 2 DIABETES

Coronary Heart Disease Risk of Patients with Prediabetes

Probably the earliest sound epidemiologic evidence of an association between prediabetes and CHD incidence as well as cardiovascular mortality comes from the Busselton study in Australia.[16] In this study, blood glucose and serum levels of insulin were measured 1 hour after an oral glucose load in addition to conventional cardiovascular risk factors. Six-year incidence of CHD and 12-year mortality from CHD and CVD were calculated in relation to baseline parameters. In men aged 60 to 69 years, having borderline or high levels of serum insulin after the 1-hour challenge showed a positive association with 6-year incidence of CHD, 12-year mortality from CHD, and 12-year mortality from CVD with risk ratios of 2.0, 2.3, and 2.4, respectively. Elevated serum insulin was





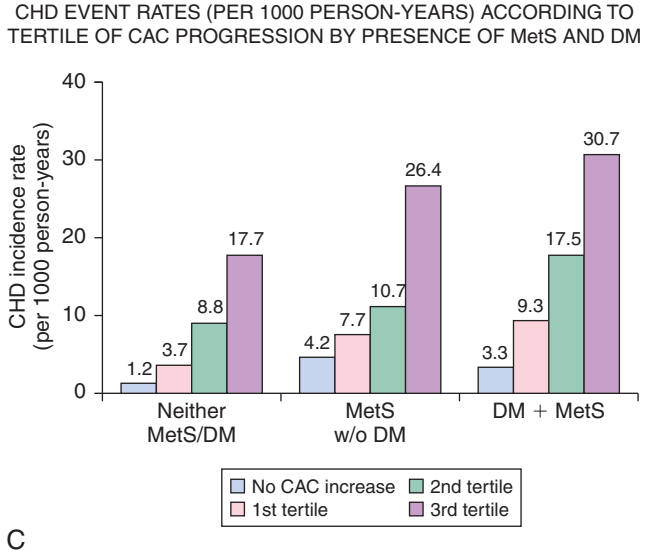


FIGURE 7-3 **A,** Incidence of CAC (per 100 person-years) according to metabolic syndrome (MetS) and diabetes (DM) status by gender among persons without baseline CAC. **B,** Progression of CAC (mean unadjusted absolute change in volume score) according to MetS and DM status by gender in persons without baseline CAC. **C,** CHD event rates (per 1000 person-years) according to tertile of CAC progression by presence of MetS and DM. Data are not shown for persons with DM without MetS because of an insufficient number of CHD events. *(Modified from Wong ND, Nelson JC, Granston T, et al: Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study,* JACC Cardiovasc Imaging *5:358-366, 2012.)*

independently associated with cardiovascular mortality in all men, whereas in women no association could be found. Further evidence of an association between prediabetes and CVD came from two studies from Finland.[17] These authors studied 3267 men aged 40 to 59 years from the Social Insurance Institution's Coronary Heart Disease Study and 1059 men aged 30 to 59 years from the Helsinki Policemen Study. An OGTT was carried out in both studies, and in addition in the Helsinki Policemen Study plasma insulin was measured. In the first study, 4-year mortality from CHD and 4-year incidence of nonfatal MI did not show an association with 1-hour postload plasma glucose. However, in the Helsinki Policemen Study, 1-hour postload blood glucose, but not fasting or 2-hour postload blood glucose, predicted 5-year incidence of CHD endpoints in multivariable analysis. However, 1-hour and 2-hour postload plasma insulin levels both predicted CHD risk even after glucose measurements from the OGTTs were controlled for. The study of men born in 1913 and 1923 also assessed insulin resistance, as estimated with the HOMA equation, and other risk factors for CHD in elderly men and followed them for 8 years.[18] Compared with patients with known diabetes, who had a 2.5-fold increased risk for CHD, there was a 2.2-fold and a 2.4-fold risk among those in the highest compared with the lowest quintile of insulin resistance and fasting insulin, respectively. Further data from the Framingham Heart Study found that IFG was associated with CHD risk in women but not in men.[19] In a first systematic review by Ford and colleagues[20] based on 18 publications, IFG and IGT both were associated with only modest increases in risk for CVD. This was confirmed by two recent, more extensive meta-analyses from the Emerging Risk Factors Collaboration (ERFC) (**Fig. 7-4**),[21,22] which reported data on fasting blood glucose concentration, risk of vascular disease, but also cause-specific death in almost 700,000 and 820,000 people from 102 and 97 prospective studies, respectively. In patients without diabetes, fasting blood glucose concentrations above 100 mg/dL were associated with major causes of death, but not concentrations between 70 and 100 mg/dL. The same held true for incident CHD and stroke.

In aggregate, these data indicate that fasting blood glucose is only modestly associated with risk of vascular disease and that a level exceeding 100 mg/dL but not between 70 and 100 mg/dL is associated with death. Insulin levels may be superior in the prediction of vascular outcome in prediabetic patients.

Coronary Heart Disease Risk of Patients with Metabolic Syndrome

During the past 10 years, a large number of studies have reported on the association between the metabolic syndrome and total mortality as well as CVD morbidity and mortality. Data have come from diverse populations and have included varying definitions; however, in most studies, WHO, International Diabetes Federation (IDF), and ATP III definitions have been used. At present, there is still ongoing controversy regarding whether or not the metabolic syndrome as a whole presents incremental information above and beyond the accumulation of individual risk factors. (See also Chapter 4.)

Probably the most frequently cited report is by Lakka and colleagues[23] from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study (**Fig. 7-5**), a population-based prospective cohort of 1209 Finnish men aged 42 to 60 years who were initially free of CVD, cancer, and diabetes. In contrast to other studies, this early study used four different definitions of the metabolic syndrome and found a prevalence ranging from 8.8% to 14.3%. During an 11.4-year follow-up, men with metabolic syndrome as defined by NCEP criteria were 2.5

HAZARD RATIOS (HRs) FOR VASCULAR OUTCOMES IN PEOPLE WITH versus THOSE WITHOUT DIABETES AT BASELINE

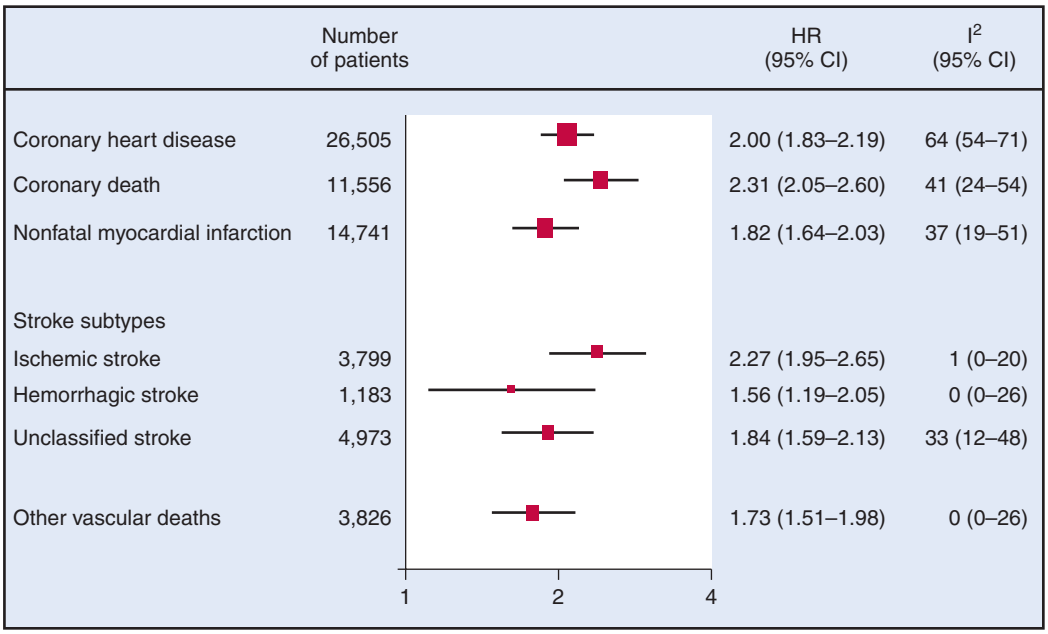


FIGURE 7-4 Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline. CI = Confidence interval; I^2 = statistic for heterogeneity. *(Modified from Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, et al: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies,* Lancet *375:2215-2222, 2010.)*

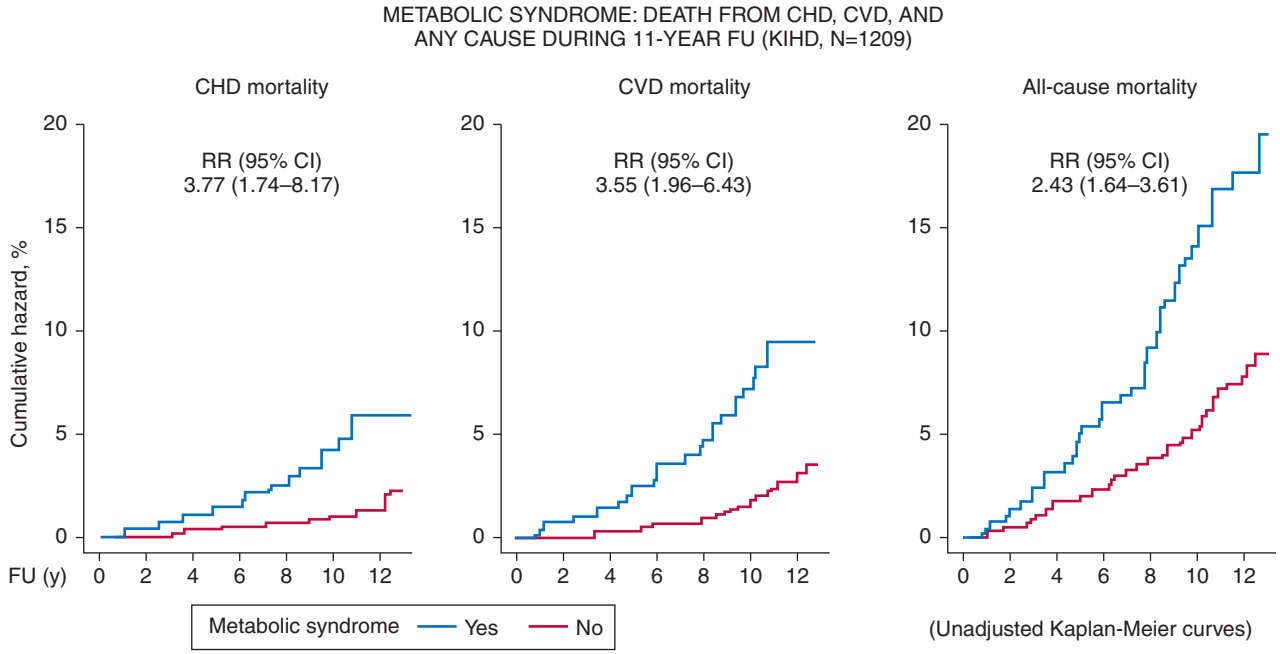


FIGURE 7-5 The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men; unadjusted Kaplan-Meier hazard curves. CI = Confidence interval; RR=relative risk. *(Data from Lakka HM, Laaksonen DE, Lakka TA, et al: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men,* JAMA *288:2709-2716, 2002.)*

times more likely to die of CHD in multivariable analysis than those defined by WHO criteria. The metabolic syndrome as defined by WHO was associated with a 2.6-fold increase in CVD mortality and a 1.9 times higher all-cause mortality. In the Botnia Study from Finland and Sweden, 4400 patients aged 35 to 70 years were studied. Risk for CHD and stroke was increased threefold in patients with metabolic syndrome, and cardiovascular mortality was markedly increased when the WHO definition was used. Microalbuminuria as an individual component was the strongest risk factor for cardiovascular death.[24] Among 12,089 black and white middle-aged individuals in the Atherosclerosis Risk in Communities (ARIC) study, the metabolic syndrome was present in 23% of those without diabetes or prevalent CVD at baseline. During 11 years of follow-up, men and women with the metabolic syndrome were approximately 1.5 and 2 times more likely to develop CHD than those without symptoms after adjustment for age, smoking, low-density lipoprotein cholesterol, and race. Similar associations were present for incident ischemic stroke. However, discrimination analysis based on the area under the curve from receiver operating characteristic (ROC) analysis did not show a clinical significant improvement once the metabolic syndrome was added to the Framingham Risk Score.[25] In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,[26] prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality were investigated in 11 prospective European cohorts comprising 6156 men and 5356 women without diabetes in the age range of 30 to 89 years. Median follow-up was 8.8 years. A modified version of the WHO definition of the metabolic syndrome was used, and to be classified as having the metabolic syndrome, patients had to have hyperinsulinemia and two or more of the following: obesity, hypertension, dyslipidemia, or impaired glucose regulation. The age-standardized prevalence of the metabolic syndrome was 15.7% in men and 14.2% in women, and hazard ratios for all-cause and cardiovascular mortality in patients with metabolic syndrome were 1.44 and 2.26 in men and 1.38 and 2.78 in women, respectively, after adjustments for age, blood cholesterol, and smoking. Data from the Framingham Heart Study provided a slightly different picture. In 3323 middle-aged patients, the prevalence of the metabolic syndrome was determined as the presence or absence of abdominal obesity, low high-density lipoprotein cholesterol (HDL-C), high triglycerides, hypertension, and IFG, and follow-up was 8 years. The presence of three or more of five criteria was seen in 26.8% of men and 16.6% of women; thus the metabolic syndrome was more prevalent in U.S. men than in European men. In men, the age-adjusted relative risk for CVD was 2.9 (for CHD it was 2.5), and for incident diabetes mellitus it was 6.9. The population attributable risk estimates were 34%, 29%, and 62% in men and 16%, 8%, and 47% in women, respectively. Thus the metabolic syndrome in this U.S. population accounted for up to one third of CVD events.[27] The considerable regional variability of the prevalence of the metabolic syndrome is evident from the Italian Longitudinal Study on Aging,[28] in which, based on ATP III criteria, the prevalence in nondiabetic men was 26% and in nondiabetic women was 15.5%. The total population comprised 5632 individuals in the age range 65 to 84 years at baseline, and CVD mortality was assessed during 4 years of follow-up. During this time period, nondiabetic men with metabolic syndrome had a 12% higher CVD mortality than those without; no significant difference was found in women. In the UKPDS 78,[29] 5102 patients with newly diagnosed type 2 diabetes were followed for a median of 10 years. Metabolic syndrome was based on ATP III, WHO, IDF, and the European Group for the Study of Insulin Resistance criteria, and was found in 61%, 38%, 54%, and 24%, respectively.

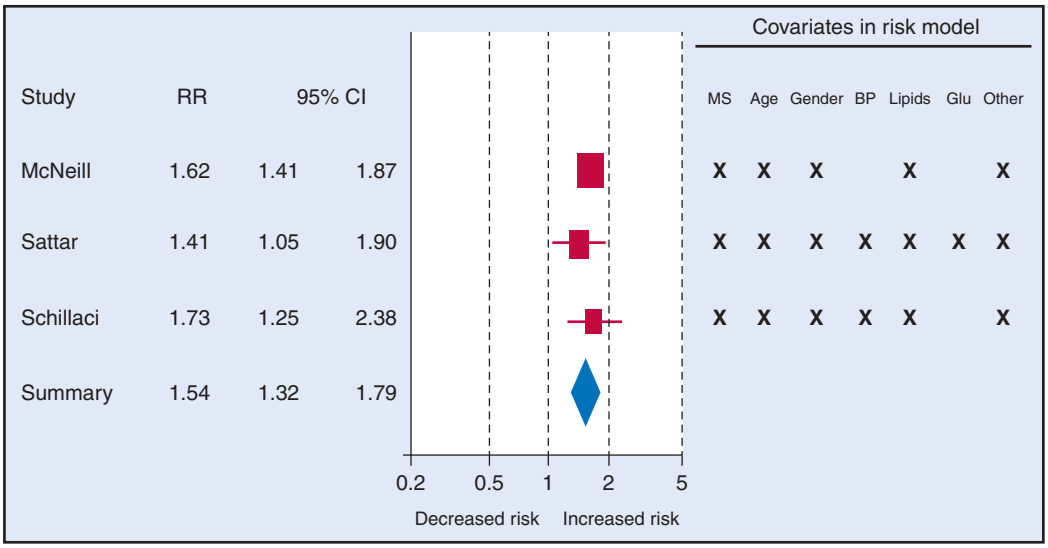


FIGURE 7-6 Relative risk (RR) and 95% confidence interval (CI) for metabolic syndrome and incident cardiovascular events and death in studies that simultaneously included metabolic syndrome and some of its components into multivariable (MV) models. BP = Blood pressure; MS = metabolic syndrome. *(Modified from Gami AS, Witt BJ, Howard DE, et al: Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies,* J Am Coll Cardiol *49:403-414, 2007.)*

Patients with metabolic syndrome had an increased risk for CVD compared with those without (the risk in those without metabolic syndrome was between 23% and 33%, depending on the definition used). However, the positive predictive value of the metabolic syndrome for CVD was only 13% to 39%. Based on such poor discrimination with respect to CVD, the authors concluded that the metabolic syndrome may be of limited clinical value for CVD risk stratification in patients with type 2 diabetes. Finally, in the Rancho Bernardo Study,[30] 977 men and 1141 women aged 40 to 94 years were recruited from 1984 to 1987 and followed for mortality for a maximum of 20 years. Various cardiometabolic biomarkers such as adiponectin, leptin, ghrelin, interleukin 6 (IL-6), and CRP were measured, and the ATP III definition of the metabolic syndrome was used. There was a crude 65% increased risk for CHD in those with metabolic syndrome. This association did not significantly decrease after adjustment for adiponectin, leptin, and ghrelin but was attenuated by 25% after adjustment for IL-6 and CRP. Thus the authors concluded that these adiposity-signaling hormones and markers of inflammation explain little of the association between the metabolic syndrome and CHD mortality. Finally, in a systematic review and meta-analysis of longitudinal studies, Gami and colleagues[31] found 37 eligible studies with 43 cohorts. The association between metabolic syndrome and cardiovascular events was stronger in women, in studies enrolling lower-risk individuals, and in studies using the WHO definition. Most important, the association remained statistically significant after adjustment for traditional cardiovascular risk factors, with a relative risk of 1.54 (**Fig. 7-6**).

Thus, despite an ongoing controversy, the aggregate data suggest a modest independent association between the metabolic syndrome and incidence of various cardiovascular outcomes. In addition to its potential role as a risk marker, the metabolic syndrome may serve as an important educational tool.

Coronary Heart Disease Risk of Patients with Type 2 Diabetes (Diabetes as a Coronary Heart Disease Equivalent)

The pronounced increased risk of diabetic patients for CVD was first reported in 1979 based on 20 years of surveillance of the Framingham cohort, which revealed a twofold to threefold increased risk of atherosclerotic complications in various vascular beds, the strongest impact being seen on intermittent claudication.[32] The study with the greatest impact on our awareness of an increased risk for cardiovascular complications in patients with diabetes, which consecutively led to the notion of diabetes as a CHD equivalent, came from a population-based case-control study published by Haffner and colleagues (**Fig. 7-7**).[33] Based on a 7-year

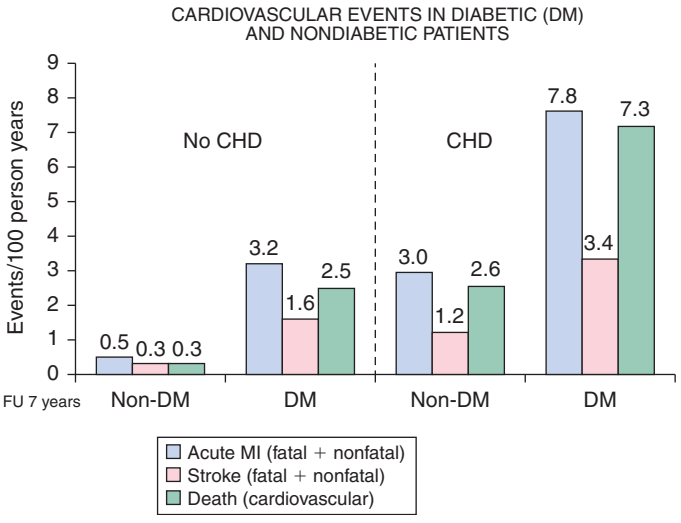


FIGURE 7-7 Incidence of cardiovascular events during a 7-year follow-up in relation to history of MI in patients with type 2 diabetes and in nondiabetic patients. *(Data from Haffner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in patients with type 2 diabetes and in nondiabetic patients with and without prior myocardial infarction,* N Engl J Med *339:229-234, 1998.)*

follow-up of 1373 nondiabetic patients and 1059 diabetic patients, the incidence rates for nonfatal and fatal MI in nondiabetic patients with and without prior MI at baseline were 18.8% and 3.5%, respectively, whereas in diabetic patients with and without prior MI they were 45% and 22%, respectively. Thus, the incidence in nondiabetic patients with prior MI was similar to that in diabetic patients without prior MI. This was also seen for nonfatal and fatal stroke and for cardiovascular death. Analyses from the large Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry provided a similar result for total mortality as an outcome variable (**Fig. 7-8**). The relative risk of death over 2 years was 1.99 (95% confidence interval [CI] 1.52-2.60) for patients with diabetes and no prior CVD, and it was 1.71 (95% CI 1.44-2.04) for patients without diabetes but prior CVD.[34] However, further studies with more rigorous definitions of MI patients and diabetes showed a considerably lower risk in patients with diabetes but without CVD compared with patients after MI but without diabetes. In the study by Evans and colleagues,[35] 3402 patients with newly diagnosed type 2 diabetes and 5350 patients in the post–acute MI period were recruited and followed for more than 10 years. Compared with patients with diabetes, the post-MI group had an almost threefold increased risk of death and an approximately threefold increased risk of hospitalization with a recurrent MI. This result was supported by data from the population-based ARIC study,[36] in which 13,719 African American and white men and women in the age range 45 to 74 years were studied from 1987 to 1989. In multivariable models, patients with a history of MI but without diabetes at baseline had a 1.9-times risk of fatal and nonfatal MI and a 1.8-times increased risk of CHD mortality compared with patients with diabetes without a prior history of MI. Yet stroke risk was similar between diabetic patients without MI and nondiabetic patients with MI. These data suggest that patients with diabetes are at increased risk for cardiovascular complications, but this risk is lower and not identical to the one of patients who have already experienced a CHD event. Looking at trends of cardiovascular complications in diabetic patients,[37] despite the increased risk compared with patients without diabetes, those with diabetes had an approximately 50% reduction in the rate of incident CVD, as was seen in nondiabetic participants although on a higher absolute level. More recently, Wannamethee and colleagues[38] looked into the impact of diabetes duration on CVD risk and all-cause mortality in older men. In their prospective analysis based on more than 4000 men aged 60 to 79 years of age with a follow-up of 9 years, the authors could demonstrate that patients with both early and late onset of diabetes had a significantly increased risk of major CHD and CVD events and all-cause mortality compared with nondiabetic men who had no history of MI, even with multivariable adjustments including novel risk biomarkers such as CRP, von Willebrand factor, and renal dysfunction. However, men with early-onset diabetes, defined as onset before the age of 60 years and a duration longer than 10 years, had a somewhat similar risk compared with men with prior MI without diabetes. Thus the duration of diabetes plays an important role, and only those with longstanding disease, based on these data, may be considered to have a CHD equivalent (**Fig. 7-9**).

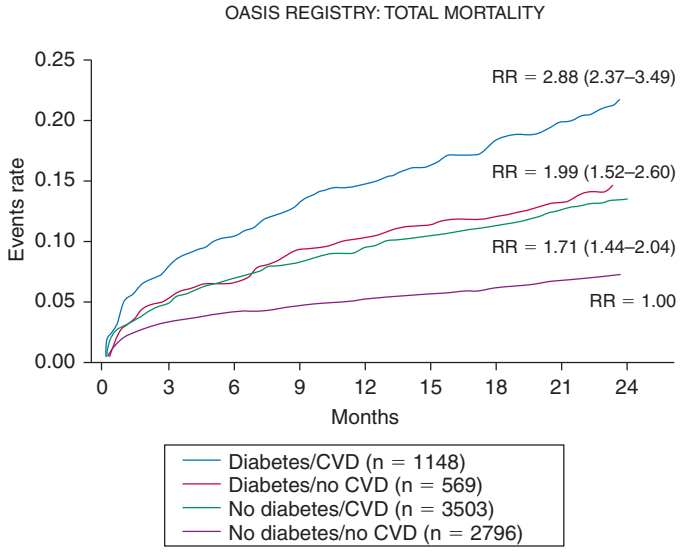


FIGURE 7-8 Total mortality: cumulative event curves for patients with and without diabetes in relation to previously known CVD. *(Modified from Malmberg K, Yusuf S, Gerstein HC, et al: Impact of diabetes on long-term prognosis in patients with unstable angina and non–Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry,* Circulation *102:1014-1019, 2000.)*

These epidemiologic data are supported by mechanistic studies coming from a prospective registry of diabetic patients undergoing diagnostic coronary angiography and IVUS in whom, in addition to the presence and extension of plaque as assessed by grayscale information, an IVUS-derived modality, virtual histology (VH), was used. Patients with diabetes duration of 10 years or longer showed a greater plaque burden in most diseased segments; also, the proportion of IVUS-defined thin-cap fibroatheroma (TCFA) in those with longstanding diabetes was greater than in those with diabetes duration of less than 10 years. This association was present even with multivariable adjustments taking into account clinical characteristics and treatment modalities.[39]

An earlier meta-analysis[40] based on 37 prospective cohorts comprising almost 450,000 patients showed that the rate of fatal CHD was higher in patients with diabetes than in those without (5.4% versus 1.6%). In addition, this meta-analysis confirmed data from the Framingham study that women with diabetes have a 50% higher risk for a fatal CHD than men, which may be explained to some extent by a more extensive adverse risk profile and in addition by differences in treatment. Two more recent meta-analyses by the ERFC (**Fig. 7-10**)[21,22] clearly demonstrated that diabetes was associated with a twofold excess risk for a wide range of vascular diseases independently from conventional risk factors. This study was based on almost 700,000 patients from whom individual data were available and in whom more than 50,000 fatal and nonfatal vascular outcomes had occurred. Of note, in addition to adjustment for conventional risk factors, in this meta-analysis, data on inflammatory and renal markers were also available that did not significantly attenuate the association. This large database also clearly showed that the impact of diabetes is not restricted to vascular complications such as CHD, stroke, peripheral artery disease (PAD), and vascular death, but diabetes also affects a variety of other causes of death including cancers, infectious diseases, renal and liver disease, and finally mental disorders.

In addition to the solid evidence from numerous long-term prospective epidemiologic studies showing that the presence of diabetes mellitus is associated with adverse vascular and nonvascular outcomes, there are also detailed

DURATION OF DIABETES IN MEN w/o PREV. MI AND ADJ. HRs OF MAJOR CVD EVENTS AND ALL-CAUSE MORTALITY

	Duration of Diabetes Mellitus in Years		
	0–1	2–7	≥ 8
No. of participants	202	103	109
CVD events			
Rate per 1000 person-years (No. of events)	20.3(32)	19.7(16)	36.6(29)
Age-adjusted HR (95% CI)	1 [Reference]	1.14(0.78–1.67)	1.39(0.98–1.96)
Adjusted HR (95% CI)*	1 [Reference]	1.19(0.79–1.80)	1.49(1.03–2.16)
All-cause mortality			
Rate per 1000 person-years (No. of events)	38.0(60)	44.4(36)	66.9(53)
Age-adjusted HR (95% CI)	1 [Reference]	1.10(0.85–1.43)	1.35(1.06–1.70)
Adjusted HR (95% CI)*	1 [Reference]	1.10(0.83–1.47)	1.39(1.07–1.79)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio; MI, myocardial infarction.
CVD events include nonfatal MI or CVD deaths.
*Adjusted for age, smoking, alcohol consumption, social class, body mass index, physical activity, stroke, systolic blood pressure, high-density lipoprotein and total cholesterol levels, low forced expiratory volume in 1 second, estimated glomerular filtration rate, C-reactive protein level, and von Willebrand factor level.

Rates per 1000 person-years, men aged 60–79 yrs

FIGURE 7-9 Duration of diabetes in 414 diabetic men without previous MI aged 60 to 79 years and rates per 1000 person-years and adjusted HRs of major CVD events and all-cause mortality. *(Modified from Wannamethee SG, Shaper AG, Whincup PH, et al: Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors,* Arch Intern Med *171:404-410, 2011.)*

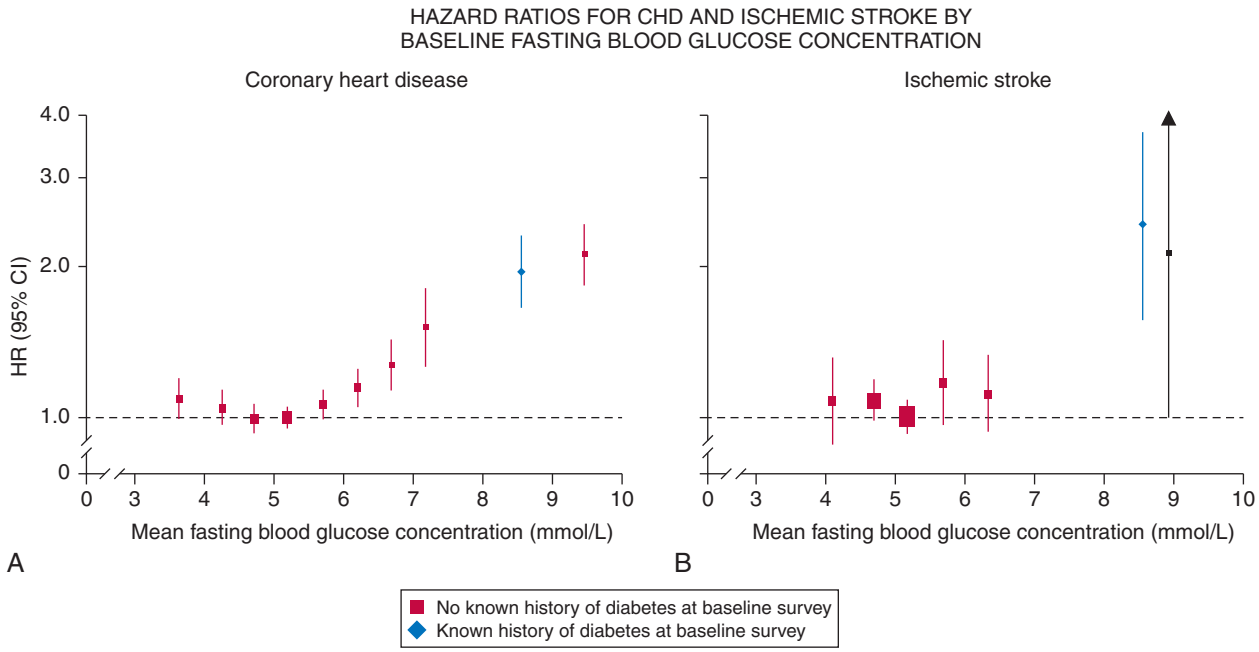


FIGURE 7-10 Hazard ratios for coronary heart disease and ischemic stroke by baseline fasting blood glucose concentration. *(Modified from Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, et al: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies,* Lancet *375:2215-2222, 2010.)*

data regarding long-term metabolic control, as assessed by hemoglobin A1c (HbA1c), in patients with type 2 diabetes and its association with macrovascular complications such as MI, stroke, amputation, and total mortality. Such data were reported first from UKPDS 35.[41] In this large prospective study the incidence of clinical complications was significantly associated with glycemia, demonstrating that each 1% reduction in mean HbA1c was associated with reductions in risk of 21% for any endpoint related to diabetes, 21% for deaths, and 40% for MI. Thus the degree of hyperglycemia seems to be strongly related to vascular outcome and all-cause mortality. These data were confirmed in another population-based cohort study from Norfolk, United Kingdom: the European Prospective Investigation into Cancer

and Nutrition (EPIC).[42] The database comprised 4662 men aged 45 to 79 years who had HbA1c measured at baseline in 1995 to 1997 and were followed until 1999. The primary outcome of interest was a composite of mortality from all causes, CVD, and ischemic heart disease. Men with manifest diabetes had a 3.5-fold increased risk of death from all causes, a more than 8-fold increased risk for cardiovascular mortality, and a 10-fold increased risk for CHD compared with patients with an HbA1c of less than 5%. However, within several categories of HbA1c from below 5% to above 7%, there was a gradual increase for all of the above-mentioned endpoints, suggesting that even in the normal upper range of HbA1c an increased risk of death or nonfatal coronary complications is present. Data from the large ARIC study based on more than 11,000 African American or white adults also demonstrated that HbA1c values at baseline were associated with newly diagnosed diabetes and cardiovascular outcomes (**Fig. 7-11**). Similar to EPIC Norfolk, this study also showed an increased risk for diabetes and cardiovascular outcome even in the normal range for HbA1c, but the increase in risk was particularly pronounced in those with an HbA1c of 6.5% or greater. Similar results were found for CHD and for stroke.[43] However, in one study with a high prevalence of diabetes, the Strong Heart Study,[44] in which HbA1c and fasting plasma glucose were measured in more than 4500 Native American adults, neither HbA1c nor fasting blood glucose added to conventional cardiovascular risk factors in the prediction of CHD or total CVD.

To summarize, there is clear evidence from a large number of well-controlled prospective epidemiologic studies, that the presence of type 2 diabetes is associated with an approximately twofold increased risk for various cardiovascular complications. In those with diabetes, the long-term control of glucose metabolism seems to play an important role because a strong relationship has been seen in several studies between HbA1c levels and cardiovascular outcome as well as total mortality.

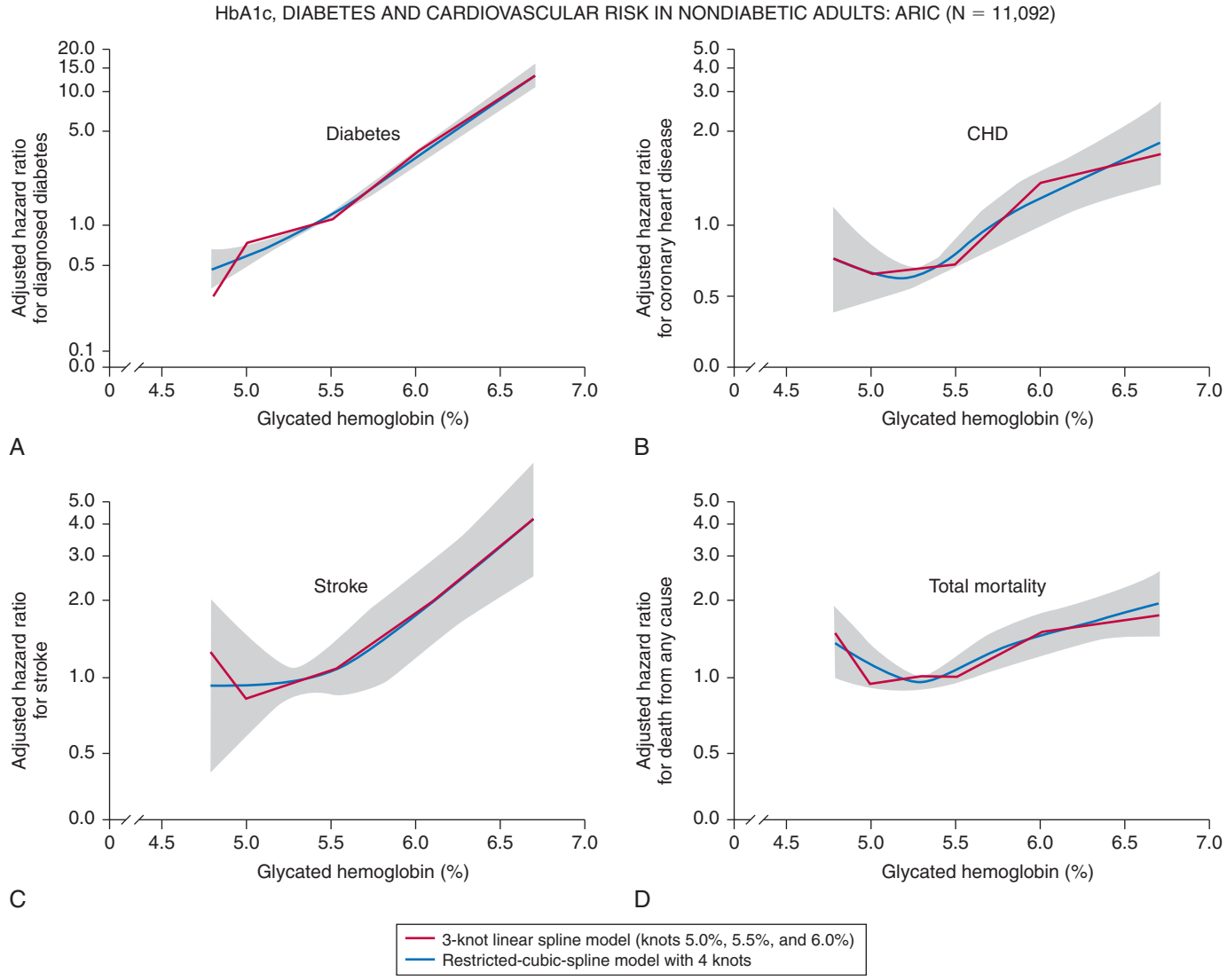


FIGURE 7-11 Adjusted HRs for self-reported diagnosed diabetes and CHD, ischemic stroke, and death from any cause, according to the baseline glycated hemoglobin value. *(Data from Selvin E, Steffes MW, Zhu H, et al: Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults,* N Engl J Med *362:800-811, 2010.)*



SHORT-TERM AND LONG-TERM PROGNOSIS AFTER ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH PATHOLOGIC GLUCOSE METABOLISM AND AFTER CORONARY INTERVENTIONS OR WITH HEART FAILURE

An ACS, in particular MI (non–ST-segment MI [NSTEMI] or ST-segment MI [STEMI]) is associated with a profound stimulation of the sympathetic nerve system (SNS). Because the SNS adversely affects glucose metabolism, a number of studies have looked into admission blood glucose in patients without manifest diabetes and its relation to in-hospital complications and long-term outcome. Stranders and colleagues[45] studied 846 patients for a median of 15 months. An increase of 18 mg/dL in admission blood glucose was associated with a 4% increase in mortality in nondiabetic and 5% in diabetic patients. Thus, admission blood glucose was similarly associated with long-term risk in nondiabetic as well as diabetic patients. This result is not surprising, given the fact that abnormal glucose tolerance and the metabolic syndrome are common risk factors in patients with acute MI. In one study, two thirds of patients after an MI had abnormal glucose tolerance at discharge compared with only 35% in controls.[46] In another study, almost 50% showed metabolic syndrome on admission to the hospital with an ACS, which was a strong and independent predictor of in-hospital case fatality but also severe heart failure.[47] In a nationwide sample of elderly patients (n = 142,000) hospitalized for acute MI in the United States from 1994 to 1996, higher glucose levels were clearly associated with a greater risk for 30-day mortality in patients without known diabetes compared with those with diabetes. In contrast, among diabetic patients, higher mortality was observed only in those with very high glucose levels (>240 mg/dL) (**Table 7-1**).[48] In a population-based MI registry, MONICA/KORA Augsburg, the authors studied admission blood glucose levels in 1631 nondiabetic and 659 diabetic patients and related admission levels to 30-day as well as 1- and 3-year case fatality. Blood glucose levels on admission were divided into quartiles, and patients without known diabetes in the top quartile (≥150 mg/dL) showed an almost threefold risk of death during in-hospital stay in multivariable analysis. In patients with type 2 diabetes mellitus, a similar relationship was seen in age- and gender-adjusted analysis, but once treatment was taken into account, as well as in-hospital complications, there was only a trend for an increased in-hospital case fatality that was no longer statistically significant. With regard to 1- and 3-year outcomes after exclusion of those who died within 28 days, only a nonsignificant trend was seen in patients without diabetes, whereas no effect was found in diabetic patients. After 3 years, no association with increased risk of death was seen for patients without or with diabetes.[49] Data from the same population-based registry[50] have demonstrated in more than 2200 patients admitted with MI from 1985 to 1992 an increased 28-day as well as 5-year mortality in diabetic patients versus nondiabetic patients (12.6% versus 7.3% at 28 days). Five-year mortality was increased by 64% in diabetic patients compared with non–diabetic patients. McGuire and colleagues[51] demonstrated in 12,142 patients from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) study presenting with the whole spectrum of ACS that diabetic patients had an increased overall risk of death or reinfarction, whether they presented with STEMI or NSTEMI, at 30 days and at 6 months. Furthermore, a large number of observational studies and reports from large randomized trials consistently have shown an increased risk for adverse cardiovascular outcomes in patients with the admission diagnosis of diabetes during in-hospital stay or long term.[34,52–54]

In addition, diabetes was a strong predictor of adverse outcome in patients admitted with an ACS who underwent coronary revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[55] Similar data have been reported from the Prevention of Restenosis with Tranilast and Its Outcomes (PRESTO) trial for PCI in stable patients[56] and from a large dataset of stable patients who underwent CABG.[57] Finally, in 1241 patients with congestive heart failure,[58] a statistically significant impact of diabetes on cardiac survival was seen. Specifically, diabetes was an independent predictor of cardiovascular mortality in ischemic patients but not in nonischemic patients.

In summary, patients with known IGT, metabolic syndrome, manifest type 2 diabetes, or even stress-induced hyperglycemia during an acute coronary event are at

TABLE 7-1 Effect of Admission Glucose on Mortality After Multivariable Adjustment

	HR* (95% CI)			
	Glucose >110-140 mg/dL	Glucose >110-170 mg/dL	Glucose >170-240 mg/dL	Glucose >240 mg/dL
All Patients[†]				
30-day mortality	1.13 (1.08-1.19)	1.31 (1.24-1.38)	1.52 (1.44-1.60)	1.77 (1.68-1.87)
1-year mortality	1.07 (1.03-1.10)	1.17 (1.13-1.21)	1.31 (1.27-1.36)	1.46 (1.41-1.52)
In Patients Without Known Diabetes[‡]				
30-day mortality	1.17 (1.11-1.24)	1.37 (1.29-1.44)	1.63 (1.54-1.73)	1.87 (1.75-2.00)
1-year mortality	1.09 (1.05-1.13)	1.20 (1.16-1.25)	1.37 (1.31-1.43)	1.56 (1.48-1.63)
In Patients With Diabetes[§]				
30-day mortality	0.90 (0.78-1.04)	0.99 (0.86-1.13)	1.09 (0.97-1.24)	1.32 (1.17-1.49)
1-year mortality	0.96 (0.87-1.06)	0.95 (0.86-1.04)	1.04 (0.96-1.14)	1.16 (1.07-1.26)

*Risk-adjusted hazard ratio (HR) with its respective 95% CI.
[†]All patients with admission glucose ≤110 mg/dL (referent group).
[‡]Patients without recognized diabetes and admission glucose ≤110 mg/dL (referent group).
[§]Patients with diabetes and admission glucose ≤110 mg/dL (referent group).
Data from Kosiborod M, Rathore SS, Inzucchi SE, et al: Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes, *Circulation* 111:3078-3086, 2005.

increased risk for short-term and long-term complications including vascular death. Diabetes mellitus also remains a strong risk factor for adverse outcome in coronary interventions such as PCI and CABG whether during an emergency situation or in stable patients. Finally, in patients with complications from MI, such as congestive heart failure, diabetes represents a strong risk factor for future outcome, in particular in ischemic cardiomyopathy.

PERIPHERAL ARTERIAL DISEASE AND DIABETES

Early data from the Framingham study have previously suggested that diabetes may be particularly strongly related to peripheral arterial disease (PAD).[32] The risk for PAD is usually twofold to fourfold increased in diabetic compared with nondiabetic patients.[59] Similar to associations observed between diabetes and CAD, the duration and severity of diabetes determine the incidence and extent of PAD.[60] Of note, as also seen in the coronary arterial tree, PAD associated with diabetes is usually characterized by more diffuse and more distal lesions than in patients without diabetes. Data from the large National Health and Nutrition Examination Survey (NHANES) study (1999 to 2204) in a total of 7058 patients 40 years and older showed the highest prevalence of PAD among older adults, non-Hispanics, blacks, and women. In multivariable analysis, in particular diabetes but also hypertension, chronic kidney disease, and smoking were strong risk factors after age, gender, and racial and ethnic differences were taken into account.[61] On a national U.S. level, approximately 2.4 million to 3.6 million diabetic patients have PAD.[62] Based on noninvasive assessment using the ABI, approximately 20% to 30% of patients with diabetes have prevalent PAD (defined as an ABI below 0.9). Similar to associations in the coronary arterial tree, in UKPDS the duration of diabetes and the degree of glycemic control were independent risk factors for PAD.[63] In addition, African Americans and patients of Hispanic descent with diabetes were at increased risk of PAD.[64] Approximately one fourth of diabetic patients with PAD demonstrate progression of symptoms over a 5-year period and an amputation rate of approximately 4%. Whereas in general, PAD symptoms are stable, there is a striking increase in CHD events over the same time period with a 20% nonfatal MI and stroke rate and a 30% death rate.[65] Clearly, the prevalence of PAD differs in relation to the comorbidity present in the individual patient. Thus, increased prevalence of PAD has been reported in patients with diabetes mellitus and arterial hypertension and in particular with chronic kidney disease or even more pronounced end-stage renal disease. Furthermore, in these subgroups the degree of blood glucose control as assessed by HbA1c was strongly increased, with risk of development of PAD and finally the necessity for limb amputation.[66]

In summary, diabetes is associated with an increased risk of PAD, and the degree of blood glucose control is associated with the severity of outcome. However, most diabetic patients have asymptomatic PAD and only approximately 20% are symptomatic. In terms of vessel distribution, PAD is more diffuse and distally located. A clustering of additional risk factors in diabetic patients may strongly contribute to more extensive and severe PAD.

DIABETES AND CORONARY HEART DISEASE IN WOMEN

Since the first publications from Framingham, the risk of coronary or in general cardiovascular complications has been reported to be higher in women compared with men by approximately 50%. In addition, during the acute phase of an ischemic event, the risk of death is higher in women than in men despite taking into account age and potential differences in treatment strategies. There are several well-controlled prospective epidemiologic studies that have looked into gender differences in diabetic patients with regard to fatal or nonfatal cardiovascular outcome. In the Rancho Bernardo Study,[67] during a 14-year follow-up in men and women aged 40 to 79 years, the relative risk for ischemic heart disease in diabetic versus nondiabetic patients was 1.8 in men and 3.3 in women after adjustment for age, and 1.9 in men and 3.3 in women after adjustment for age, systolic blood pressure, cholesterol, body mass index (BMI), and cigarette smoking. This gender difference may largely be explained by a persistently more favorable survival rate of women than men without diabetes. Yet, no convincing pathophysiologic explanation had been suggested. In the British Regional Heart Study and the British Women's Heart Health Study, Wannamethee and colleagues[68] looked into a large panel of traditional and more novel risk markers such as insulin resistance, inflammation, activated coagulation, and endothelial dysfunction in 7529 men and women aged 60 to 79 years with no previous MI. Nondiabetic women clearly tended to have a more favorable risk factor profile—which, however, was attenuated in the diabetic state. Waist circumference, BMI, level of von Willebrand factor, white blood cell count, insulin resistance, diastolic blood pressure, HDL-C, tissue plasminogen activator (t-PA), and factor VIII level differed more between diabetic and nondiabetic women than between diabetic and nondiabetic men. Thus the more extensive risk factor profile in women may account for the increased risk of CVD. It is interesting to note that in the Heart and Estrogen/Progestin Replacement Study (HERS)[69] in women with CHD, hormonal replacement reduced the incidence of diabetes by 35%. The intake of estrogen and progestin in postmenopausal women improved their metabolic profile, but based on other adverse effects, in particular an increase in breast cancer incidence,[70] hormonal replacement cannot be recommended for this purpose. Further data suggest a particularly increased risk in women with diabetes who developed complications after MI such as congestive heart failure. In a study of more than 900 patients, of whom 41% were female, the increased risk of death in diabetic patients appeared to be particularly prominent in women.[71]

In summary, data from several epidemiologic studies and registries indicate that women with diabetes have a higher risk for cardiovascular complications during the acute event but also long term. This may at least in part be a result of the well-known age difference in the occurrence of a first MI between genders, but may also be a result of late diagnosis of acute ischemic events in women and also of differences in treatment strategies—which, at present, are diminishing. In addition, in particular in elderly women the risk factor profile seems to be more extensive than in diabetic men, which may provide an additional explanation for differences in relevant outcomes. However, other gender-specific differences may still play a role, but this area needs further investigation.



DIABETES AND ATHEROSCLEROTIC COMPLICATIONS: GEOGRAPHIC AND ETHNIC DIFFERENCES

Because of the obesity epidemic and the rapid acquisition of the Western lifestyle in many Asian countries and Latin-America, the prevalence and incidence of diabetes are increasing dramatically worldwide, with a much more profound increase in former developing countries compared with established industrialized societies. An increase of 42% has been estimated for the time period between 1995 and 2025 in developed countries, and an approximately 170% increase in developing countries during the same time period. Thus in 2025 there will be more than 300 million people with diabetes in the adult population worldwide, with approximately 230 million in developing countries and approximately 70 million in developed countries.[72] In 2025 the highest prevalence will be seen in former socialist economies of Europe, in countries in the Middle East, in Latin-America and the Caribbean, in India, and finally in Western societies with prevalence rates of 6% to 9%. In terms of absolute numbers, the Middle East and India will be leading, followed by Western countries, China, and Latin America. More recent global estimates based on larger studies from 91 countries suggest that in the population aged 20 to 79 years there will be an increase in the prevalence of diabetes from 6.4% in 2010 (285 million adults) to 7.7% (439 million adults) in 2030. Developing countries will face a 70% increase compared with a 20% increase in industrialized societies.[73] As a consequence, subclinical atherosclerosis and clinical complications from atherosclerosis will increase dramatically.

Thus there are pronounced geographic and ethnic differences in type 2 diabetes incidence, which may be explained by different socioeconomic situations and cultural conditions but also by the well-known susceptibility for insulin resistance in Southeast Asians.

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8 Pathology of Diabetic Atherosclerosis

Composition, Characteristics, and Distribution



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Diabetes mellitus is associated with the development of accelerated atherosclerotic coronary artery disease, which results in increased morbidity and mortality from cardiovascular complications including acute myocardial infarction and stroke.[1,2] Atherothrombosis is the leading cause of death worldwide despite major progress in the understanding of the role of traditional risk factors in its etiopathogenesis.[3]

In this chapter we address morphologic characteristics of coronary and carotid plaques in individuals with type 1 and 2 diabetes as compared with those without diabetes, and we discuss the involvement of endothelial cells, macrophages, and smooth muscle cells as well as the signaling transduction receptors for advanced glycation endproducts (RAGEs) that accumulate in diabetes and are associated with acceleration of atherosclerosis.

PLAQUE MORPHOLOGY AND INFLAMMATION IN DIABETIC ATHEROSCLEROSIS

Diabetes is associated with increased prevalence of hyperlipidemia, hypertension, obesity, and a hypercoagulable state, all of which contribute to higher incidence of coronary, carotid, and peripheral artery diseases that are associated with high mortality and morbidity, as reviewed in Chapters 7, 27, and 28.

Coronary and Carotid Artery Disease

Moreno and colleagues[4] have evaluated coronary atherectomy specimens obtained from 47 patients with type 2 diabetes and compared them with specimens from 48 nondiabetic individuals, and demonstrated that patients with diabetes exhibited a larger content of lipid-rich atheroma (7% ± 2%) than those without diabetes (2 ± 1%). In addition, macrophage infiltration was significantly greater in patients with diabetes (22 ± 3%) than in those without diabetes (12 ± 1%), and the incidence of thrombus was higher in individuals with diabetes (62%) than in those without diabetes (40%).

Cipollone and colleagues[5] examined carotid endarterectomy specimens from patients with type 2 diabetes (n = 30) and compared them with specimens from patients without diabetes (n = 30) and showed that the plaques from patients with diabetes were richer in macrophages and T lymphocytes and also had a more frequent expression of human leukocyte antigen–DR (HLA-DR). Immunohistochemistry revealed greater reactivity of the RAGEs in patients with diabetes versus those without diabetes, especially in areas rich in macrophages and angiogenesis. The activity of nuclear factor kappa B (NF-κB) was greater in patients with diabetes than in those without diabetes and showed a concordance with RAGE expression. Also, cyclooxygenase 2 (COX-2) membrane-associated protein eicosanoid and glutathione metabolism synthase 1 (mPGES-1), matrix metalloproteinases (MMPs), and gelatinolytic activity were increased in patients with diabetes compared with those without diabetes. Patients with diabetes had reduced collagen content and increased lipid and oxidized low-density lipoprotein content as compared with those without diabetes. In this study, RAGE, COX-2/mPGES-1, and MMP expression was linearly correlated with plasma concentration of hemoglobin A1c (HbA1c).[5] Therefore, in individuals with diabetes, RAGE overexpression along with enhanced inflammatory reaction and COX-2/mPGES-1 expression in macrophages may contribute to plaque destabilization.

The linear correlation between RAGE and HbA1c in the aforementioned study indicates that RAGE may be downregulated by improving glycemic control [5]; the same group also reported the possibility of a pharmacologic modulation of glucose-independent RAGE generation.[6] Patients with type 2 diabetes and asymptomatic carotid artery stenosis were randomized to diet plus simvastatin (40 mg/day) or diet alone for 4 months before endarterectomy. Plaques from the simvastatin group showed significantly less immunoreactivity for myeloperoxidase (MPO), AGEs, RAGE, p65, COX-2, mPGES-1, MMP-2, MMP-9, lipids, and oxidized low-density lipoprotein, along with reduced gelatinolytic activity, increased procollagen 1 and collagen content, and fewer macrophages, T lymphocytes, and HLA-DR–positive cells. RAGE inhibition by simvastatin was also identified in plaque-derived macrophages and was reverted by addition of AGEs in vitro. These results suggest that simvastatin inhibits RAGE expression by decreasing MPO-dependent AGE generation, which may contribute to plaque stabilization.

Hyperglycemia is known to increase lipolysis, which leads to the release of nonesterified fatty acids (NEFAs) into the

bloodstream.[7,8] Elevated serum levels of NEFAs are associated with vascular damage in type 2 diabetes.[9] Mas and colleagues[10] showed a significant increase in the quantity of NEFAs in carotid endarterectomy specimens retrieved from patients with type 2 diabetes as compared with those without diabetes by using time-of-flight secondary ion mass spectrometry. Although plasma levels of NEFAs were greater in patients with diabetes than in those without diabetes, tissue NEFA levels did not correlate with plasma NEFA levels. Laser-capture microdissection with quantitative reverse transcription polymerase chain reaction RT-PCR revealed that mRNA expressions of lipoprotein lipase (LPL) and monocyte chemoattractant protein 1 (MCP-1) were greater in NEFA-rich areas than in NEFA-poor areas. Conventional immunohistochemistry and in situ Southwestern hybridization also demonstrated that those with diabetes had greater protein expression of LPL and MCP-1, greater infiltration of macrophages and T lymphocytes, and greater activated NF-κB–positive nuclei than those without diabetes, where the patterns of distribution were similar to those of NEFA. These findings indicate that NEFA may be produced locally and contribute to local inflammation within the atherosclerotic plaques in patients with type 2 diabetes.

A recent study using carotid endarterectomy specimens showed that neovascularization, only in the shoulder regions of the plaques, was more frequent in patients with type 2 diabetes than in those without diabetes (52% versus 26%) with no differences in macrophage content in the entire section of the plaque.[11] In addition, patients with diabetes had greater expression of vascular endothelial growth factor receptor 2 (VEGFR-2) as compared with those without diabetes. The increased vascularization in the shoulder region suggests a higher risk of atherosclerotic vascular complications, such as plaque rupture (**Fig. 8-1**) followed by healing in patients with diabetes. These findings parallel those shown in aortic and coronary arteries of diabetic patients.

In summary, atherosclerotic plaques retrieved from patients with hyperglycemia (diabetes) show a higher expression of AGE and its receptor RAGE on endothelial and smooth muscle cells, which are involved in the induction of plaques that are highly inflamed with greater infiltration by macrophages, T cells, and HLA-DR-positive cells. Patients with diabetes show vascular dysfunction that likely occurs from increased production of reactive oxygen species as well as activation of platelet. Furthermore, carotid plaques from individuals with diabetes have demonstrated higher expression of protein kinase C (PKC) and NF-κB, with large necrotic cores, hemorrhage, and an increase in angiogenesis, especially in the shoulder regions. In addition, patients with diabetes had greater expression of VEGFR-2 than those without diabetes. These carotid plaques have highly expressed MPO, p65, COX-2, mPGES-1, MMP-2, MMP-9, lipids, and oxidized low-density lipoprotein, along with an increase in gelatinolytic activity and greater collagen content (**Fig. 8-2**).

Coronary Atherosclerosis in Sudden Death

Sudden death victims with type 2 diabetes show greater prevalence of coronary artery disease as a cause of death than those without diabetes (**Fig. 8-3A**). We have reported

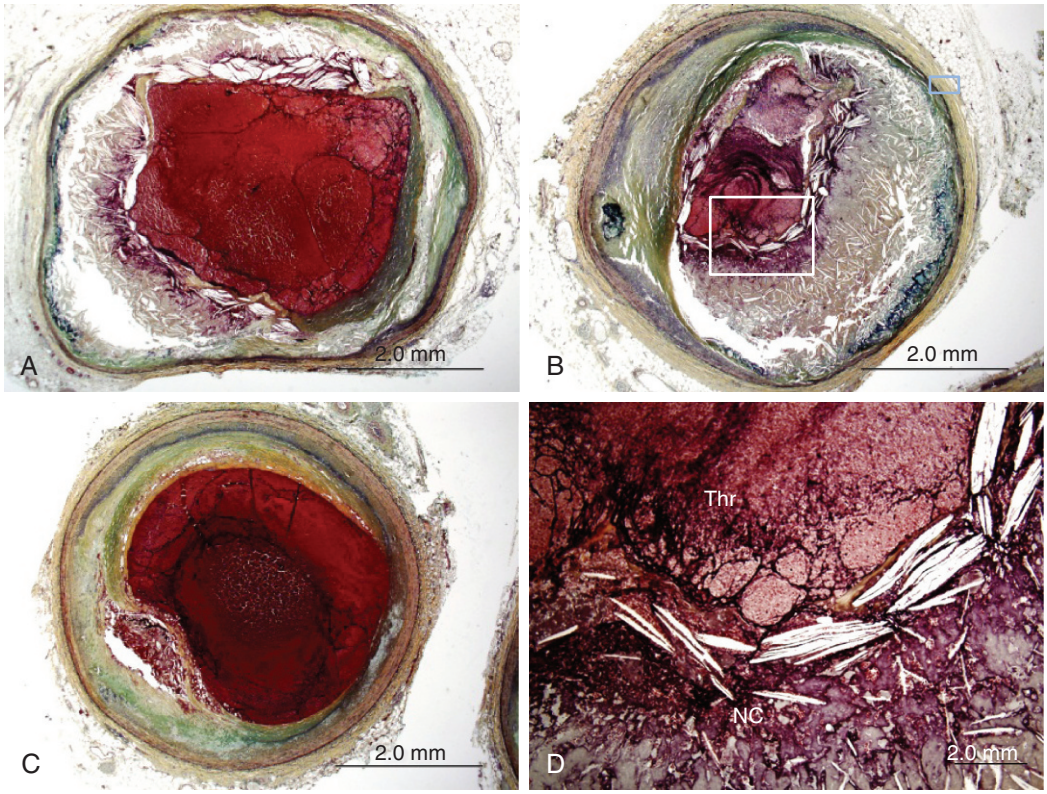


FIGURE 8-1 Acute plaque rupture with occlusive thrombus. **A** to **C,** Serial histologic sections of acute plaque rupture with occlusive thrombus in the proximal right coronary artery from a 59-year-old man who died suddenly. Proximal **(A)** and middle **(B)** lesions show underlying large necrotic core with almost total absence of fibrous cap, and destroyed medial wall. **C,** Distal lesion with propagated occlusive thrombus. **D,** A high-power magnification image of the white box in **B** shows thrombus (Thr) with underlying necrotic core (NC) where the fibrous cap is absent. (***B*** *and* ***D*** *reproduced with permission from Falk E, Nakano M, Bentzon JF, et al: Update on acute coronary syndromes: the pathologists' view,* Eur Heart J *34:719-728, 2013.)*

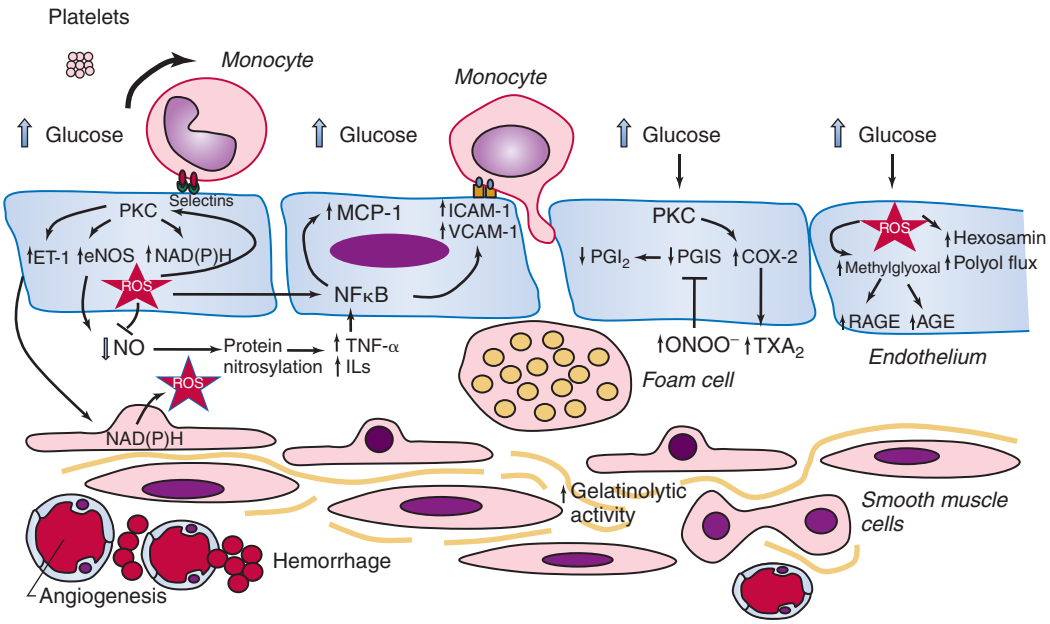


FIGURE 8-2 Mechanisms of hyperglycemia-induced vascular damage. High intracellular glucose concentrations lead to PKC activation and subsequent ROS production by NAD(P)H oxidase and $p66^{Shc}$ adaptor protein. Increased oxidative stress rapidly inactivates NO, leading to formation of the pro-oxidant $ONOO^-$ responsible for protein nitrosylation. Reduced NO availability is also caused by PKC-dependent eNOS deregulation. Indeed, PKC triggers enzyme upregulation, thus enhancing eNOS uncoupling and leading to a further accumulation of free radicals. On the other hand, hyperglycemia reduces eNOS activity, blunting activatory phosphorylation at Ser1177. Together with the lack of NO, glucose-induced PKC activation causes increased synthesis of ET-1, favoring vasoconstriction and platelet aggregation. Accumulation of superoxide anion also triggers upregulation of proinflammatory genes MCP-1, VCAM-1, and ICAM-1 via activation of NF-κB signaling. These events lead to monocyte adhesion, rolling, and diapedesis with formation of foam cells in the subendothelial layer. Foam cell–derived inflammatory cytokines maintain vascular inflammation as well as proliferation of smooth muscle cells, accelerating the atherosclerotic process. Endothelial dysfunction in diabetes also derives from increased synthesis of TXA_2 via upregulation of COX-2 and inactivation of PGIS by increased nitrosylation. Furthermore, ROSs increase the synthesis of glucose metabolite methylglyoxal, leading to activation of AGE and RAGE signaling and the pro-oxidant hexosamine and polyol pathway flux. There is increased angiogenesis with greater expression of VEGFR-2, and hemorrhages within plaques. Furthermore, both an increase in collagen deposition and greater gelatinolytic activity occur. AGE = Advanced glycation endproduct; COX-2 = cyclooxygenase-2; eNOS = endothelial nitric oxide synthase; ET-1 = endothelin 1; ICAM-1 = intracellular cell adhesion molecule 1; ILs = interleukins; MCP-1 = monocyte chemoattractant protein 1; NAD(P)H = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; $ONOO^-$ = peroxynitrite; PGI_2 = prostacyclin; PGIS = prostacyclin synthase; PKC = protein kinase C; RAGE = the receptor for AGEs; ROS = reactive oxygen species; TNF-α = tumor necrosis factor α; TXA_2 = thromboxane A2; VCAM-1 = vascular cell adhesion molecule 1. *(Modified from Paneni F, Beckman JA, Creager MA, Cosentino F: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I,* Eur Heart J *34:2436-2443, 2013; with permission.)*

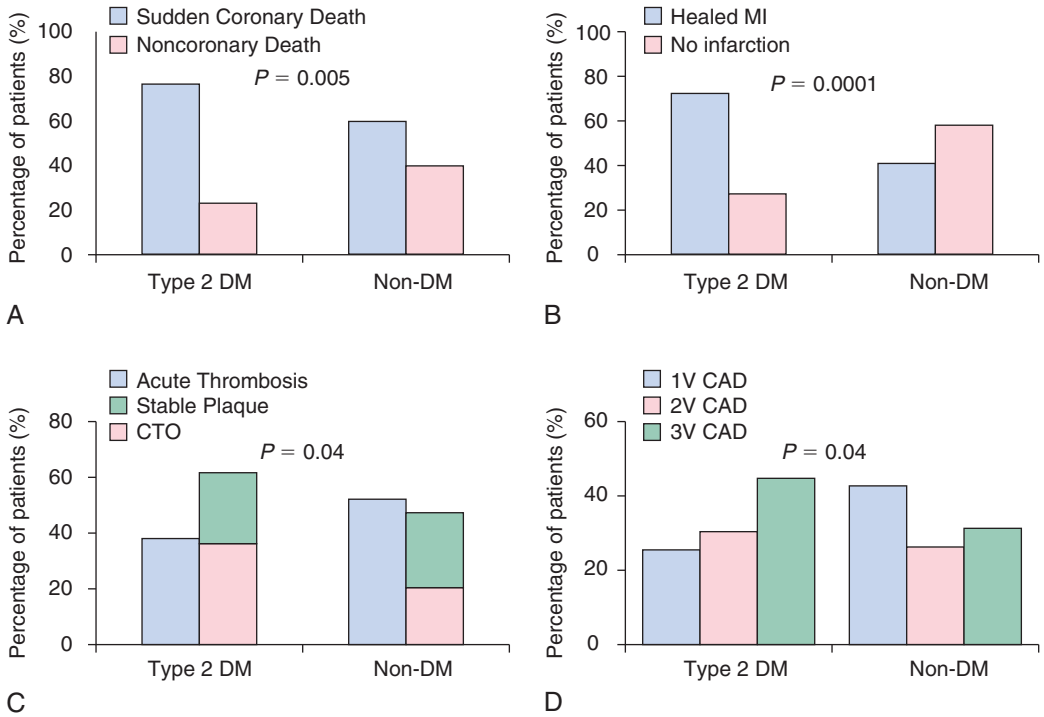


FIGURE 8-3 Extent of coronary artery disease (CAD) in sudden death victims with and without diabetes mellitus (DM). A, Cause of death in sudden death victims with type 2 diabetes is more frequently attributed to coronary atherosclerotic disease than in those without diabetes. **B,** Healed myocardial infarction (MI) is more prevalent in patients with type 2 diabetes than in those without diabetes. **C,** The incidence of acute thrombi in patients with type 2 diabetes was lower than in those without diabetes, whereas stable severe coronary artery disease and chronic total occlusion (CTO) were more frequently observed in patients with type 2 diabetes than in those without diabetes. **D,** Coronary atherosclerosis in patients with type 2 diabetes was more extensive than in those without diabetes. Approximately half of patients with diabetes showed triple vessel disease, whereas in those without diabetes, single-vessel disease was more frequent than double- or triple-vessel disease.

morphologic findings in patients with type 1 and those with type 2 diabetes and compared them with age- and gender-matched individuals without diabetes who died suddenly from coronary artery atherosclerotic disease.[12] The underlying inclusion criterion for sudden coronary death was presence of an acute coronary thrombus or severe epicardial coronary atherosclerosis (>75% cross-sectional area luminal narrowing) of one or more major arteries and the absence of noncoronary causes of death at autopsy.

Sixty-six individuals with diabetes were selected on the basis of history of type 1 diabetes mellitus treated with insulin or the presence of type 2 diabetes. Type 2 diabetes was ascertained by history of oral hypoglycemics or postmortem glycohemoglobin 10% or higher in the absence of type 1 diabetes. A total of 16 patients with type 1 diabetes and 50 with type 2 diabetes were included. The findings in these patients were compared with 66 age- and gender-matched individuals without diabetes who died from severe coronary artery disease (**Table 8-1**). The prevalence of smoking and hypertension in patients with type 1 and type 2 diabetes was comparable to the prevalence in those without diabetes. The body mass index (BMI) in individuals with type 2 diabetes (30.5 ± 7.4 kg/m^2) was significantly greater than in those without diabetes (26.6 ± 5.4 kg/m^2, $P = 0.001$), whereas in individuals with type 1 diabetes BMI (25.6 ± 6.4 kg/m^2) was similar to that in patients without diabetes ($P = 0.7$). Individuals with type 2 diabetes showed a trend toward higher levels of total cholesterol (TC) and lower levels of high-density lipoprotein cholesterol (HDL-C) than those without diabetes (TC 227 ± 83 versus 211 ± 79 mg/dL, $P = 0.3$; HDL-C 33 ± 16 versus 38 ± 18 mg/dL, $P = 0.1$). The ratio of TC to HDL-C was significantly higher in individuals with type 2 diabetes than in those without diabetes (7.9 ± 3.9 versus 6.3 ± 3.4, $P = 0.02$). On the contrary, individuals with type 1 diabetes had a trend toward lower levels of TC (183 ± 52 mg/dL) and comparable levels of HDL-C (37 ± 14 mg/dL) and TC-to–HDL-C ratio (5.8 ± 2.9) relative to those without diabetes.

The percent necrotic core area (necrotic core area divided by plaque area) was greater in individuals with type 1 ($12.0\% \pm 5.7\%$) and type 2 ($11.6\% \pm 8.4\%$) diabetes than in those without diabetes ($9.4\% \pm 9.3\%$; $P = 0.05$ versus type 1, $P = 0.004$ versus type 2 diabetics) (**Table 8-2**). The percent calcified area was greater in individuals with type 2 diabetes ($12.1\% \pm 11.2\%$) than in those without diabetes ($11.4\% \pm 13.5\%$, $P = 0.05$), and individuals with type 1 diabetes had a comparable percent calcified area ($7.8\% \pm 9.1\%$) compared with those without diabetes. The number of fibroatheromas was greater in individuals with type 2 diabetes (8.8 ± 4.3) than in those without diabetes (6.9 ± 4.7, $P = 0.02$), whereas those with type 1 diabetes had a similar number of fibroatheromas (7.1 ± 5.0) compared with those without diabetes. The number of thin-cap fibroatheromas was comparable among the groups. The number of healed plaque ruptures in individuals with type 2 diabetes was greater than in those without diabetes (2.6 ± 1.8 versus 1.9 ± 1.8, $P = 0.04$), while those with type 1 diabetes only showed a trend toward a greater number of healed ruptures (2.6 ± 2.1) as compared with those without diabetes.

By multivariable analysis (**Table 8-3**) there was a positive correlation between mean percent necrotic core area and glycohemoglobin, independent of HDL-C, ratio of TC to HDL-C, age, smoking, and gender ($T = 2.8$, $P = 0.005$). Similarly, the ratio of TC to HDL-C ($T = 2.5$, $P = 0.01$) and BMI ($T = 3.5$, $P = 0.006$) correlated positively with percent necrotic core area. There was a significant relationship between numbers of fibroatheroma and ratio of TC to HDL-C ($T = 3.0$, $P = 0.0003$). Glycohemoglobin correlated positively with number of fibroatheromas, although the relationship was not statistically significant ($T = 1.7$, $P = 0.09$).

Macrophage plaque area and T-cell infiltration were significantly greater in individuals with diabetes than in those without diabetes ($P = 0.03$), along with HLA-DR expression (see **Table 8-2**; **Figs. 8-4** and **8-5**). The fact that T-cell infiltration was greater in individuals with type 1 diabetes is consistent with the fact that type 1 diabetes is an

TABLE 8-1 Patient Demographics, Risk Factors, and Cardiac Findings in Patients with Type 1 Diabetes and Those with Type 2 Diabetes Versus Nondiabetic Patients from Sudden Coronary Death Registry

	TYPE 1 DM (n = 16)	TYPE 2 DM (n = 50)	NON-DM (n = 66)	*P* VALUE (TYPE 1 DM VERSUS NON-DM)	*P* VALUE (TYPE 2 DM VERSUS NON-DM)
Age (year)	50.3 ± 13.2	50.2 ± 11.0	50.6 ± 12.3	0.9	0.9
Women	25%	30%	29%	0.8	0.9
Blacks	20%	30%	29%	0.7	0.9
HbA1c (%)	12.2 ± 2.5	10.7 ± 2.6	6.2 ± 0.6	0.0001	0.0001
Smokers	42%	58%	55%	0.4	0.8
Hypertension	29%	35%	30%	0.9	0.6
Body mass index (kg/m^2)	25.6 ± 6.4	30.5 ± 7.4	26.6 ± 5.4	0.7	0.001
TC (mg/dL)	183 ± 52	227 ± 83	211 ± 79	0.3	0.3
HDL cholesterol (mg/dL)	37 ± 14	33 ± 16	38 ± 18	0.8	0.1
TC/HDL cholesterol	5.8 ± 2.9	7.9 ± 3.9	6.3 ± 3.4	0.7	0.02
Heart weight (g)	425 ± 119	524 ± 140	434 ± 121	0.7	0.004
Corrected heart weight (g)*	428 ± 94	508 ± 134	460 ± 106	0.3	0.03
Healed infarcts	33%	73%	37%	0.7	0.0001

Values are expressed as mean ± standard deviation or percentage.
DM = diabetes mellitus; HDL = high-density lipoprotein; TC = total cholesterol.
*Corrected for body weight.
Data from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study, *Arterioscler Thromb Vasc Biol* 24:1266-1271, 2004.

TABLE 8-2 Plaque Characteristics in Patients with Type 1 Diabetes and Those with Type 2 Diabetes Versus Nondiabetic Patients from Sudden Coronary Death Registry

	TYPE 1 DM (n = 16)	TYPE 2 DM (n = 50)	NON-DM (n = 66)	*P* VALUE (TYPE 1 DM VERSUS NON-DM)	*P* VALUE (TYPE 2 DM VERSUS NON-DM)
Acute coronary thrombi	21%	42%	51%	0.03	0.2
Acute plaque rupture	6%	32%	27%	0.09	0.6
Plaque erosion	6%	12%	29%	0.02	0.04
Necrotic core area (%)*	12.0 ± 5.7	11.6 ± 8.4	9.4 ± 9.3	0.05†	0.004†
Calcified matrix area (%)*	7.8 ± 9.1	12.1 ± 11.2	11.4 ± 13.5	0.9†	0.05†
Fibroatheroma (n)	7.1 ± 5.0	8.8 ± 4.3	6.9 ± 4.7	0.9	0.02
Thin-cap fibroatheroma (n)	1.0 ± 1.3	0.8 ± 0.8	0.7 ± 0.8	0.5	0.8
Healed plaque rupture (n)	2.6 ± 2.1	2.6 ± 1.8	1.9 ± 1.8	0.2	0.04
Total plaque burden (%)	275 ± 129	358 ± 114	232 ± 128	0.04	0.0001
Distal plaque burden (%)	310 ± 114	630 ± 263	331 ± 199	0.8	0.0001
Macrophage area (mm^2)	0.15 ± 0.02	0.13 ± 0.03	0.10 ± 0.02‡	0.03†	0.03†

Values are expressed as mean ± standard deviation or percentage.
DM = diabetes mellitus.
*Divided by plaque area.
†*P* values calculated using log-normalized data.
‡*P* = 0.006 versus type 1 and 2 diabetes combined.
Data from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study, *Arterioscler Thromb Vasc Biol* 24:1266-1271, 2004.

TABLE 8-3 Relationship of Risk Factors, Including Diabetes, to Plaque Characteristics: A Multivariate Analysis

INDEPENDENT VARIABLES (RISK FACTORS)	% NECROTIC CORE AREA*		NUMBER OF FIBROATHEROMAS†		% MACROPHAGE AREA‡	
	T	*P VALUE*	*T*	*P VALUE*	*T*	*P VALUE*
Glycohemoglobin (%)	2.8	0.005	1.7	0.09	2.9	0.004
TC/HDL cholesterol	2.5	0.01	3.0	0.0003	1.3	0.19
Body mass index	3.5	0.006	0.57	0.57	1.5	0.14
Smoking	−0.4	0.7	−1.1	0.24	−0.6	0.5
Age	−1.2	0.2	−1.2	0.2	−5.4	0.0001

The population for this table is the 132 patients with three separate one-way analysis of variance (ANOVA) analyses correlating three dependent variables (mean % necrotic core area, mean % macrophage area).
*Mean percent necrotic core area (of the four arteries studies per patient).
†Mean number of fibroatheromas per heart.
‡Mean macrophage area (of the four arteries per patient).
Data from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study, *Arterioscler Thromb Vasc Biol* 24:1266-1271, 2004.

autoimmune disease with a common genetic susceptibility to other disorders, like autoimmune thyroiditis, which may also be of pathophysiological significance in coronary plaque pathology.[13] There was a strong positive correlation between macrophage area and glycohemoglobin, independent of HDL-C, ratio of TC to HDL-C, age, smoking, and gender (T = 2.9, $P = 0.004$) (see **Table 8-3**). The combined effect of hypercholesterolemia and diabetes on macrophage infiltration and necrotic core size were further evaluated. The degree of macrophage infiltrate and necrotic core size as assessed by morphometry were significantly greater in diabetic patients with normal cholesterol or hyperlipidemia as compared to nondiabetic patients (**Fig. 8-6**).

Acute Coronary Thrombosis

The incidence of acute thrombi was significantly less in individuals with type 1 diabetes (21%) than in those without diabetes (51%, $P = 0.03$) in sudden coronary death victims (see **Table 8-2**). Individuals with type 1 diabetes showed a trend toward lower incidence of acute plaque rupture than those without diabetes (6% versus 27%, $P = 0.09$), and plaque erosion was significantly less frequent in individuals with type 1 and type 2 diabetes than in those without diabetes (6%, 12% versus 29%, $P = 0.02$ and $P = 0.04$). The incidence of acute thrombi in individuals with type 2 diabetes was lower than in those without diabetes, whereas stable severe coronary artery disease and chronic total occlusion were more frequently observed in individuals with type 2 diabetes than in those without diabetes (see **Fig. 8-3C**). The incidence of acute plaque rupture in individuals with type 2 diabetes (32%) was comparable to that in individuals without diabetes (27%).

Diffuse Coronary Atherosclerosis

In sudden death victims, approximately half of individuals with diabetes showed triple-vessel disease, whereas those without diabetes had a higher prevalence of single-vessel disease (see **Fig. 8-3D**). To further evaluate the extent of coronary atherosclerosis, plaque burden was calculated by adding the maximal percent cross-sectional area luminal narrowing in four main arterial beds—that is, the left main, left anterior descending, left circumflex, and right coronary arteries.[14] A similar number was obtained for distal arteries. Total plaque burden was significantly greater in individuals with type 2 diabetes than in those without diabetes

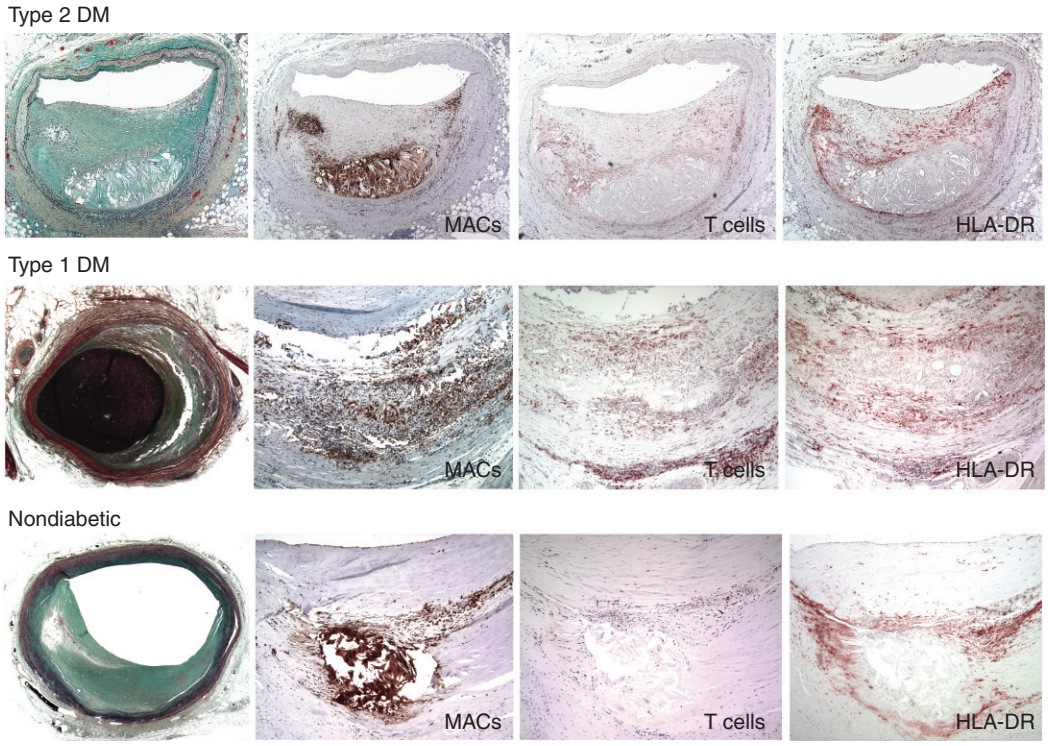


FIGURE 8-4 Inflammation in diabetic coronary arteries. Coronary fibroatheromas illustrating the extent of macrophages (CD68), T cells (CD45RO), and HLA-DR expression in patients with type 1 and 2 diabetes mellitus (DM) and nondiabetic patients. *(Modified from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study,* Arterioscler Thromb Vasc Biol *24:1266-1271, 2004.)*

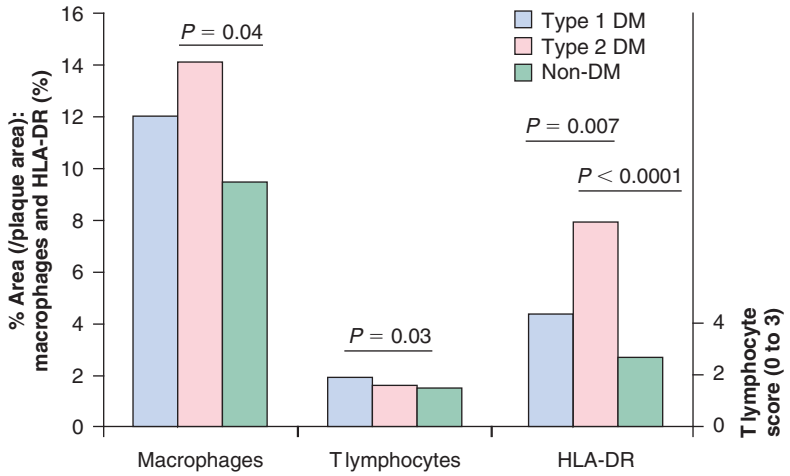


FIGURE 8-5 Comparison of inflammatory infiltrate in patients with diabetes versus those without diabetes. Bar graph showing quantitative and semiquantitative comparisons of the extent of macrophages, T lymphocytes, and HLA-DR expression in coronary arteries from patients with diabetes and those without diabetes. Plaque macrophages and HLA expression were greater in patients with diabetes (type 1 and 2) than in those without diabetes, whereas T-cell infiltration was maximal in patients with type 1 diabetes. *(Modified from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study,* Arterioscler Thromb Vasc Biol *24:1266-1271, 2004.)*

(358 ± 114 versus 232 ± 128, $P = 0.0001$), and distal plaque burden was also significantly greater in individuals with type 2 diabetes than in those without diabetes (630 ± 263 versus 331 ± 199, $P = 0.0001$) (see **Table 8-2**). Individuals with type 1 diabetes showed greater total plaque burden (275 ± 129) than those without diabetes ($P = 0.04$), whereas distal plaque burden in individuals with type 1 diabetes (310 ± 114) was comparable to that in individuals without diabetes ($P = 0.8$). Thus, individuals with type 2 diabetes who died suddenly with severe coronary disease had extensive coronary atherosclerosis, including distal involvement, as compared with those without diabetes. Part of the reason for increased plaque burden may be attributed to a higher rate of healed plaque ruptures, which may contribute to plaque progression.[15] The effect of diabetes on plaque burden has also been demonstrated by calcium imaging studies.[16] The implication of these findings is unclear, but a direct atherogenic effect of type 2 diabetes may be implicated, which is probably related to the development of lipid-rich cores. The known risk of diabetes for the late development of complications following coronary artery bypass graft surgery, which include acute myocardial infarction and graft failure,[17,18] may in part be attributable to distal disease, which may impair blood flow distal to graft anastomoses.

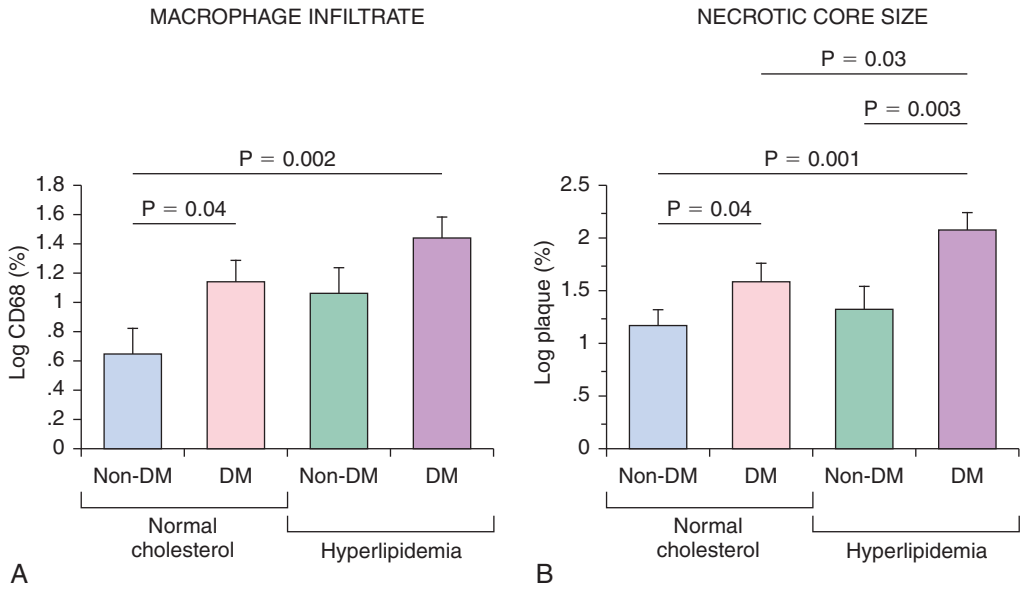


FIGURE 8-6 Combined effect of hyperlipidemia and diabetes on macrophage infiltration and necrotic core size. **A,** Combined effect on mean macrophage percent (log-normalized). **B,** Combined effect on mean necrotic core size (log-normalized). There is a significant difference between diabetic patients (DM) and nondiabetic patients (non-DM) when cases were separated by the presence or absence of hyperlipidemia. Hyperlipidemia was defined as TC over 200 mg/dL or ratio of TC to HDL-C exceeding 5. *(Modified from Burke AP, Kolodgie FD, Zieske A, et al: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study,* Arterioscler Thromb Vasc Biol *24:1266-1271, 2004.)*

Coronary Arterial Remodeling

Coronary artery remodeling was first described by Glagov in 1987 in a landmark paper showing that vessels enlarge as atherosclerotic plaque burden increases.[19] Glagov showed that vessel lumen compromise is not observed until the vessel is greater than 40% narrowed in cross-sectional area by atherosclerotic plaque. In other words, the vessel is said to be positively remodeled—that is, there is vessel enlargement, and the internal elastic lamina (IEL) area is increased (**Fig. 8-7**).[20] A vessel is negatively remodeled when the lumen area is smaller than the expected lumen, including reduction that may occur from tapering of the vessel.[21]

We have shown that the IEL area, when adjusted for the distance from the coronary ostium, was greater in individuals with type 1 and 2 diabetes than in those without diabetes (18.2 ± 6.6 mm^2, 16.5 ± 4.4 mm^2, and 16.0 ± 4.5 mm^2, respectively). The mean IEL area was also significantly greater in individuals with type 1 ($P = 0.001$) and type 2 diabetes ($P = 0.01$). By multivariable analysis, there was a correlation between individuals with type 1 diabetes and IEL area independent of heart weight, plaque area, percent necrotic core, and percent plaque calcification ($P = 0.0004$). In this analysis, percent necrotic core ($P = 0.05$), plaque area ($P < 0.0001$), and heart weight ($P = 0.05$) also showed positive correlation with IEL area.

The findings of clinical studies in patients with diabetes have been ambiguous, with some patients showing positive remodeling and others showing negative remodeling.[22,23] Our studies involving sudden coronary death victims without a known history of coronary artery disease support the notion that individuals with diabetes are more likely to show positive remodeling. However, it is possible that those who survive will eventually undergo negative remodeling, but this will require long-term follow-up either by multislice computed tomography (MSCT) or intravascular ultrasound (IVUS) studies. Our laboratory has shown that the necrotic core and macrophage infiltrates are associated with expansion of the IEL independent of plaque size and independent of diabetic status.[20] Therefore it is not surprising that sudden coronary death victims with type 1 and 2 diabetes show positive remodeling when they have greater macrophage and T-cell infiltration and larger necrotic cores as compared with those without diabetes.

Hemorrhage and Angiogenesis

Plaque hemorrhage has been shown to be associated with intraplaque angiogenesis. In type 2 diabetes, angiogenesis is increased and is associated with plaque hemorrhage and rupture.[24] Increasing intraplaque hemorrhage as assessed by glycophorin A staining of red cell membranes has been linked with plaque progression, enlarging necrotic core, greater macrophage infiltration, and iron deposition within coronary atherosclerotic plaques.[25] In type 2 diabetes, angiogenesis is increased and is associated with plaque hemorrhage and rupture.[24] Moreno and Fuster[24] showed that intraplaque hemorrhage and angiogenesis in abdominal or thoracic aorta were greater in individuals with type 2 diabetes than in those without diabetes. Intraplaque hemorrhage leads to the release of free Hb, in which iron is incorporated and acts as an oxidant, which stimulates inflammation (**Fig. 8-8**). The extent of neovascularization correlates with macrophage and T-call infiltration and plaque hemorrhage, which were greater in individuals with diabetes than in those without diabetes (**Fig. 8-9**).[26]

The untoward effects of free Hb are antagonized by Hp which binds free Hb and facilitates the uptake of Hb-Hp complexes by macrophages that have the receptors (CD163) which help remove free Hb.[27] The Hp gene has two alleles (1 and 2) giving rise to three genotypes—Hp2-2, Hp2-1, and Hp1-1—and individuals with Hp2-2 and diabetes have impaired clearance for Hb.[28] Individuals with diabetes and Hp2-2 had increased iron as compared to Hp1-1 or 2-1 (46% versus 12%). Among the nondiabetic patients with the Hp2-2 genotype, there was a nonsignificant trend toward higher prevalence of iron in plaques.[28]

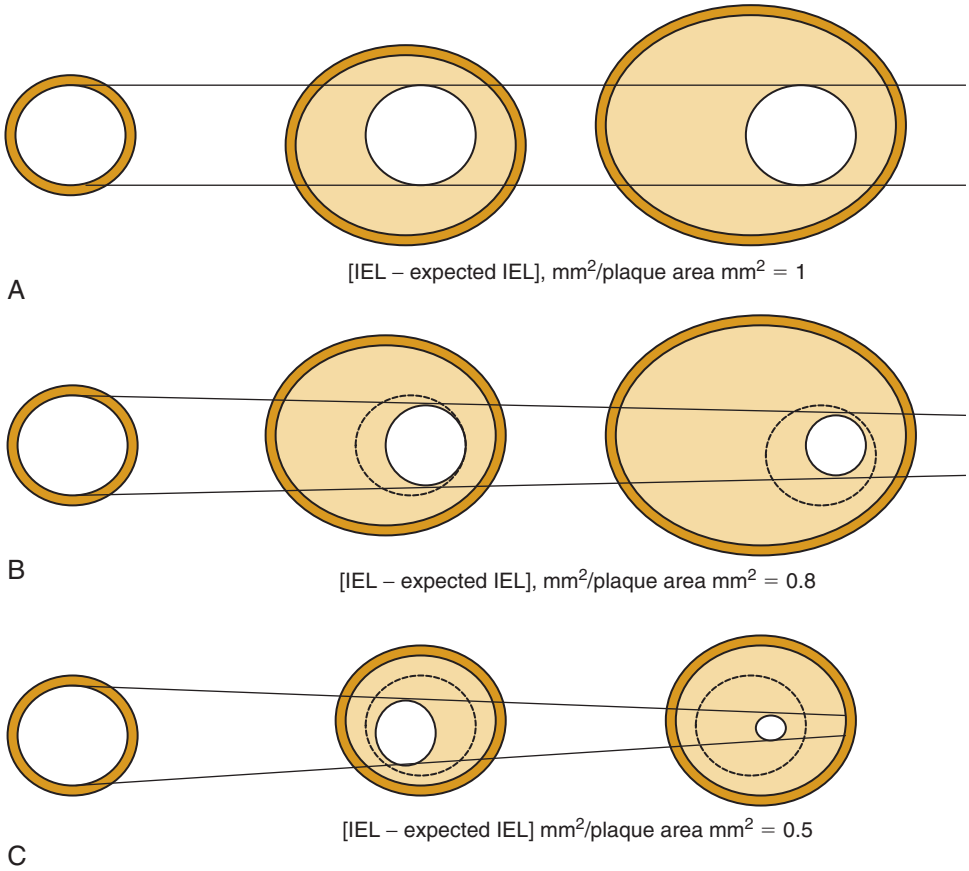


FIGURE 8-7 Method of assessing positive remodeling. The left circles indicate normal reference segments without plaque, and the two right figures are two examples of positive remodeling with an equal remodeling score. Using the formula (IEL – Expected IEL)/Plaque area, remodeling that allows no reduction in lumen with increasing plaque size **(A)** would result in a value of 1. The increase in IEL area resulting from plaque expansion is equivalent to the total plaque area. Any lesser degree of remodeling results in eventual occlusion with increased plaque area. **B,** With a score of 0.8, the increase in IEL over the predicted value is greater than the plaque area bounded by the expected IEL by a ratio of 4:1. The dotted circle represents the predicted IEL based on the reference segment. In **C,** a score of 0.5 indicates that the increase in IEL increase over expected (IEL – expected IEL) is the same as the plaque area impinging into the lumen from the expected IEL; therefore the IEL expansion is one half the plaque area. IEL = Internal elastic lamina. *(Reproduced with permission from Burke AP, Kolodgie FD, Farb A, et al: Morphological predictors of arterial remodeling in coronary atherosclerosis,* Circulation *105:297-303, 2002.*

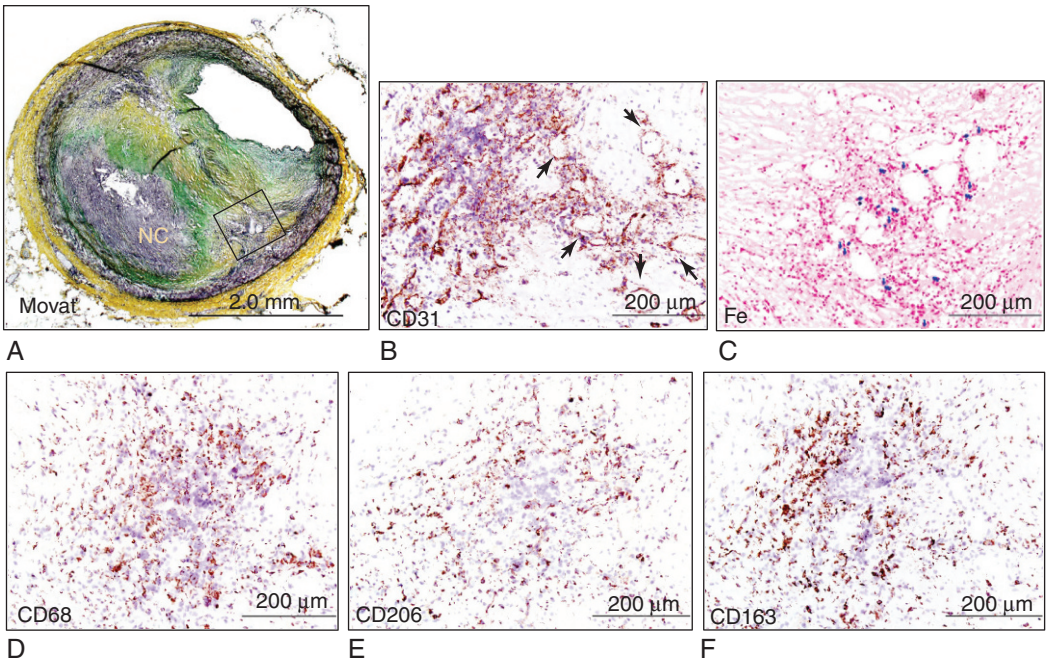


FIGURE 8-8 Angiogenesis, hemorrhage, iron deposition, and inflammation in diabetic coronary plaques. Histologic sections from a 48-year-old black man with history of hypertension and diabetes who died suddenly. **A,** A low-power image shows fibroatheroma with severe luminal narrowing and angiogenesis. **B** to **F,** High-power images of the black box in **A. B,** Note abundant CD31 (platelet endothelial cell adhesion molecule 1 [PECAM-1]) staining that indicates the presence of angiogenesis (arrows). **C,** The same area shows abundance of iron (blue), suggestive of hemorrhage. **D** to **F,** There are also abundant macrophages that are detected by CD68, CD206 (mannose receptor), and CD163 (Hb-haptoglobin receptor) staining.

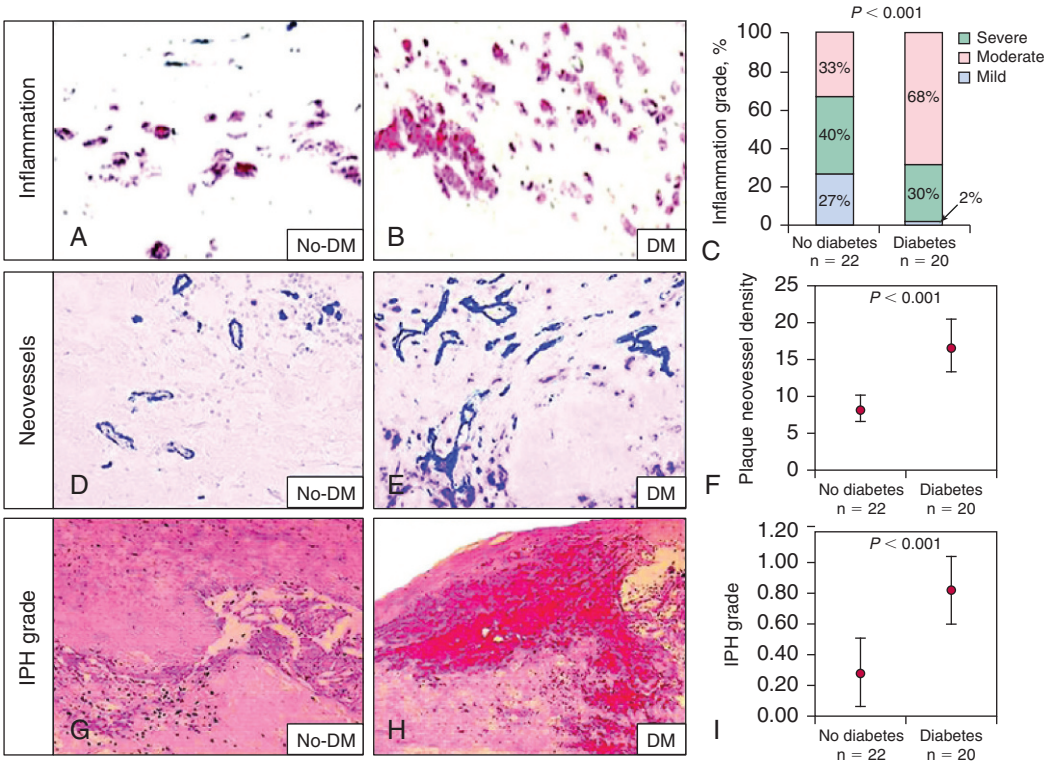


FIGURE 8-9 Inflammation, neovascularization, and intraplaque hemorrhage in aortic atherosclerosis from patients with and without diabetes. **A,** Nondiabetic atherosclerotic plaque cap stained with CD68/CD3 in red chromogen shows mild inflammation in high-power field, 40× (grade 1); less than 25 macrophages in the view. **B,** Diabetic plaque cap shows severe inflammation in high-power field, 40× (grade 2); more than 25 macrophages per field are depicted in diabetic plaque. **C,** Distribution of inflammation grade in nondiabetic and diabetic plaques. **D,** Double-label immunohistochemistry with neovessels stained by CD34 in blue chromogen and inflammatory cells stained with CD68/CD3 in red chromogen. Nondiabetic plaque shows fewer dense neovessels and inflammatory cells in the high-power field, 40×. **E,** Diabetic plaque showing more dense neovessels with tubuloluminal spaces surrounded by inflammatory cells seen in high-power field, 40×. **F,** Mean and 95% confidence interval for plaque neovessel density in nondiabetic and diabetic plaques. **G,** Nondiabetic plaque with less than 25% hemorrhage seen in high-power field (grade 1). **H,** Hematoxylin-eosin–stained diabetic plaque showing severe intraplaque hemorrhage occupying more than 75% of the plaque core seen in high-power field, 40× (grade 3). **I,** Mean and 95% confidence interval for intraplaque hemorrhage (IPH) grade in nondiabetic and diabetic plaques. *(Reproduced with permission from Purushothaman KR, Purushothaman M, Muntner P, et al: Inflammation, neovascularization and intra-plaque hemorrhage are associated with increased reparative collagen content: implication for plaque progression in diabetic atherosclerosis,* Vasc Med *16:103-108, 2011.)*

In addition, diabetic patients with the Hp2-2 genotype have been reported to have a twofold to fivefold increase in major adverse cardiovascular events as compared with diabetic patients with the Hp2-1 or Hp1 genotype.[29]

Coronary Calcification

Coronary calcification is an invariable component of atherosclerosis and is influenced by the presence of well-known risk factors.[30,31] It usually begins with the death of smooth muscle cells and macrophages and eventually also involves the necrotic core and the collagen-rich areas. Calcification has been shown to correlate with plaque burden, but there is only a weak correlation with severity of luminal narrowing.[32] The extent of calcification is also dependent on plaque type; the smallest amount of calcification is seen in plaque erosion, and the greatest in healed plaque ruptures and fibrocalcific plaques.[33] Most acute plaque ruptures show some calcification; however, almost three quarter show only speckled calcification, which is not easily detected on fluoroscopy or MSCT or IVUS. Similarly, over 50% of thin-cap fibroatheromas or vulnerable plaques show either no or speckled calcification. Several studies have demonstrated that presence of coronary calcification as identified by CT in asymptomatic individuals is a predictor of cardiac events when patients are followed for 3 to 5 years.[34–36] In patients presenting with acute coronary syndrome, coronary calcification is invariably detected, and the amount of calcification is significantly greater in acute coronary syndromes compared with age-matched controls without coronary artery disease.[37] Type 2 diabetes is associated with higher plaque burden, and a higher coronary calcium score of more than 400 by CT coronary angiography in patients with history of coronary heart disease.[38] A three-vessel optical coherence tomography study in nonculprit plaques revealed that patients with diabetes showed higher prevalence of lipid index, calcification, and thrombus than those without diabetes.[39]

MECHANISMS OF ACCELERATED ATHEROSCLEROSIS IN DIABETES

AGEs, also discussed extensively in Chapter 9, are the product of the Maillard reaction, which is a form of nonenzymatic browning that occurs from a chemical reaction between an amino acid and a reducing sugar.[40] AGEs accumulate in the tissues, especially the extracellular matrix, as well as in the plasma or serum of patients with diabetes. In vivo, in the presence of high levels of glucose, AGEs may form from multiple biochemical pathways; a major precursor of AGE is methylglyoxal (MG), which arises from nonenzymatic phosphate elimination from glyceraldehyde phosphate and dihydroxyacetone phosphate, two intermediates of glycolysis. MG is highly toxic, and therefore several detoxifying mechanisms exist, one of which is glyoxalase 1 (Glo1).[40] AGEs

have been implicated in the structural and functional alterations of proteins that form during aging and long-term hyperglycemia[41] and have been correlated with renal damage and coronary artery disease in individuals with diabetes.[12,42] The various AGEs bind a receptor for AGE (RAGE),[43] which is upregulated in diabetic glomeruli, microangiopathic disease, and atherosclerosis.[5,12,44,45] RAGE expression can be demonstrated by immunohistochemical techniques[46]; RAGE is present in atherosclerotic carotid plaques of individuals with and without diabetes.[5,47] When AGEs bind to RAGE, a diverse set of consequences ensues, namely generation of reactive oxygen species, vascular dysfunction, and inflammation (**Fig. 8-10**).[40,48] RAGE also binds to the non-AGEs such as S100A12, a member of the S100/calgranulin family, high-mobility group box 1 (HMGB1), and Mac-1 (CD11b/CD18).[40] S100A12 (also known as extracellular newly identified RAGE-binding protein [EN-RAGE]) is a proinflammatory cytokine expressed especially in macrophages and may promote inflammation within the plaque.[49,50] However, AGEs not only bind to RAGE but also to CD36 and macrophage scavenger receptors.[40]

We examined coronary atherosclerotic plaques from individuals with type 2 diabetes and those without diabetes and showed that RAGE was localized to macrophages, smooth muscle cells, erythrocytes, and endothelial cells in both; however, the overall expression of RAGE was significantly greater in individuals with diabetes. The most extensive staining for RAGE was observed in macrophages followed by smooth muscle cells, but also the intensity of staining was greater in individuals with diabetes than those without diabetes. RAGE expression is often associated with apoptotic macrophages and smooth muscle cells. Density of apoptotic nuclei surrounding the necrotic core was significantly greater in individuals with type 1 and type 2 diabetes as compared with those without diabetes. EN-RAGE expression in individuals with diabetes was most prominent in macrophages and, to a lesser degree, in smooth muscle cells in the regions surrounding the necrotic core. The role of RAGE and EN-RAGE upregulation in atherosclerotic plaque is likely complex, and the precise triggers of the inflammatory response, which culminate in the formation in plaques with large necrotic cores versus fibrocalcific plaques in the presence of hyperglycemia, remain unknown.

Experimental studies using the apolipoprotein E (apo E)–deficient mouse model of streptozotocin-induced diabetes by Bucciarelli and colleagues[51] showed that aortic atherosclerosis lesion area was increased but RAGE

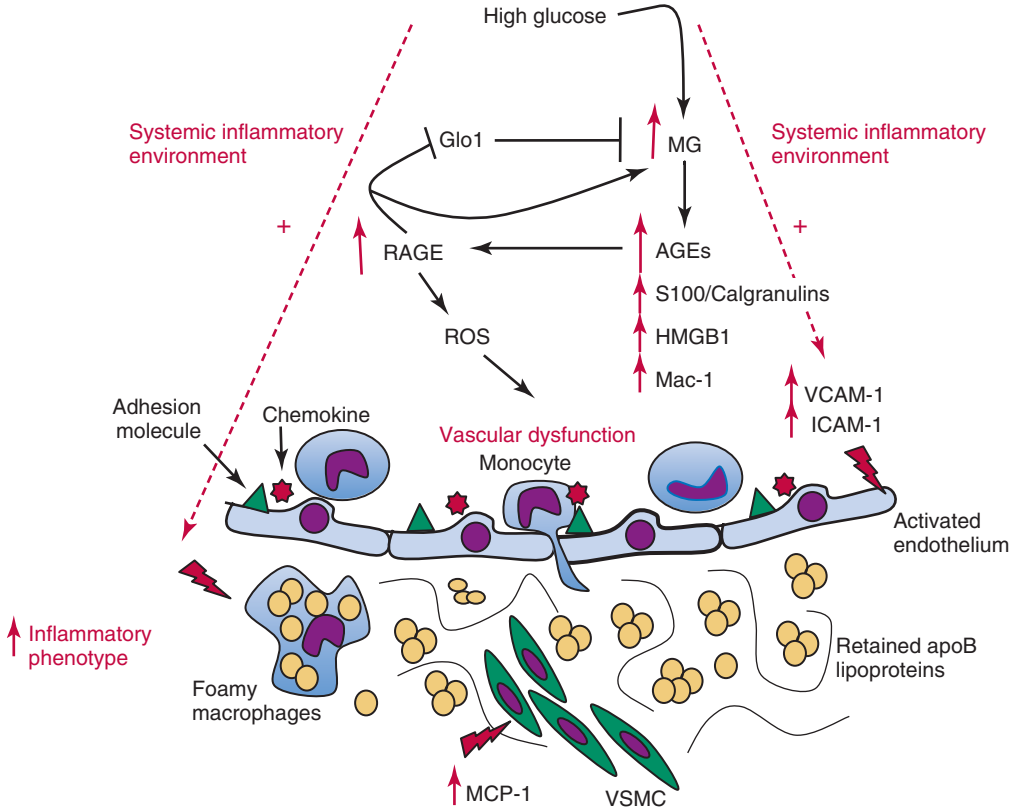


FIGURE 8-10 **Possible mechanisms through which hyperglycemia effects endothelial cells, vascular smooth muscle cells, and macrophages, promoting atherogenesis.** Hyperglycemia leads to excess production of methylglyoxal (MG), which through a series of reactions may form irreversible advanced glycation endproducts (AGEs). AGEs exhibit their actions at least in part by binding to the receptor for AGE (RAGE) and are potent generators of reactive oxygen species (ROSs), vascular dysfunction, and inflammation. RAGE also binds the non-AGEs such as S100/calgranulins, high-mobility group box 1 (HMGB1), and Mac-1 (CD11b/CD18), which are proinflammatory ligands. In addition, RAGE downregulates glyoxalase 1 (Glo1), the chief enzyme responsible for detoxifying MG. Downregulation of Glo1 suppresses MG detoxification and therefore leads to further MG-driven AGE and RAGE and ROS production, which promotes adhesion molecules (intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1]) expression on endothelial cells, and also increases the influx of monocytes and macrophages through aldose reductase (AR)–polyol pathway, or through activation of protein kinase C (PKC). In vascular smooth muscle cells (VSMCs), the principal effect of increased glucose is increased production of monocyte chemoattractant protein 1 (MCP-1), which could act in concert with the endothelial cell change to bring more monocytes into the growing lesion. The effects of hyperglycemia on both endothelial cells and macrophages are most pronounced in the presence of an inflammatory environment. apo B = apolipoprotein B. *(Reproduced and modified with permission from Ramasamy R, Yan SF, Schmidt AM: The diverse ligand repertoire of the receptor for advanced glycation endproducts and pathways to the complications of diabetes.* Vascul Pharmacol *57:160-167, 2012; and Bornfeldt KE, Tabas I: Insulin resistance, hyperglycemia, and atherosclerosis,* Cell Metabol *14:575-585, 2011.)*



blockade by soluble RAGE decreased atheroma area and complexity of lesions. Aberrant glucose metabolism is known to be mediated by several pathways, and the polyol pathway by aldose reductase (AR) has been postulated to be one of them. Vedantham and colleagues[52] showed that transgenic mice expressing human AR crossed on to apo E −/− streptozotocin-induced diabetic mice had increased atherosclerotic lesion size. In addition, pharmacologic inhibition of AR resulted in reduced lesion size.[52] Hyperglycemia has been shown to accelerate influx of inflammatory markers through the transforming growth factor beta (TGF-β) signaling pathway and focal adhesion pathway in apo E–null mice even before the development of atherosclerotic lesions.[53] Glucose-induced endothelial dysfunction has been shown to be related to activation of PKC in the rat mesenteric model that resulted in endothelial expression of P-selectin and intercellular adhesion molecule (ICAM) (see **Figs. 8-2** and **8-11**). This effect could be blocked by superoxide dismutase enzyme of bisindolylmaleimide-I, thus showing the importance of oxidative stress in hyperglycemia.[54]

Although these findings indicate the important role of inflammation and metabolic abnormalities in accelerated atherosclerosis in diabetes, increased risk of atherothrombosis in patients with diabetes as shown in clinical studies may also be attributed to increased thrombogenicity despite extensive glycemic control, reviewed extensively in Chapter 10. Hernández Vera et al[55] showed that lean normoglycemic rats transplanted with diabetic rat bone marrow had increased thrombosis with normal glucose levels, whereas diabetic rats transplanted with lean normoglycemic control bone marrow showed reduced thrombosis despite the presence of hyperglycemia. Rats with increased thrombosis had significantly greater platelet volume, activated and reticulated platelets, increased turnover and production of platelets, reduced expression of platelet-endoplasmic reticulum stress proteins (protein disulfide isomerase and 78-kDa glucose-regulated protein), and increased tissue factor procoagulant activity, as compared with lean normoglycemic controls.[55] These results suggest that hematopoietic-derived blood alterations as well as inflammation and accelerated atherosclerosis contribute to the increased risk of atherothrombosis in patients with diabetes.

SUMMARY

Severe coronary atherosclerosis in individuals with diabetes is accompanied by the presence of healed myocardial infarction and cardiomegaly. Diabetes-induced coronary artery disease is associated with greater inflammatory infiltrate (macrophages and T lymphocytes), larger necrotic core size, and diffuse atherosclerosis. The mechanism of inflammation in diabetic animal models as well as in humans is related to greater expression of AGE and its receptor RAGE. RAGE also binds to the non-AGEs such as the S100/calgranulin family, HMGB1, and Mac-1, which are proinflammatory mediators that promote inflammation and vascular dysfunction in patients with diabetes. Plaque angiogenesis and hemorrhage are more prevalent in individuals with diabetes, and the receptor for Hb-Hp complexes (CD163) helps remove free Hb, in which iron is incorporated and acts as an oxidant and inflammatory stimulus. Further studies are needed to better understand the relationship of hyperglycemia and insulin resistance that lead to acceleration of atherosclerosis.

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9 Vascular Biology of Atherosclerosis in Patients with Diabetes

Hyperglycemia, Insulin Resistance, and Hyperinsulinemia

Ravichandran Ramasamy, Shi Fang Yan, and Ann Marie Schmidt

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DIABETES AND ACCELERATED ATHEROSCLEROSIS

Scope and Complexity of the Problem

One of the most deadly complications of types 1 and 2 diabetes is accelerated atherosclerosis, the consequences of which include more frequent and more deadly heart attacks and strokes, as well as myocardial dysfunction. The latter occurs both secondary to myocardial infarctions and as a result of innate diabetes-mediated damage to the myocardium. With the worldwide rise in both types 1 and 2 diabetes, an epidemic of cardiovascular complications in diabetes is almost certainly on the horizon.[1] Together with the cost of affected individuals' productivity and the very high costs to already heavily burdened health care systems, the cardiovascular complications of diabetes have many potentially devastating consequences for personal well-being and global economies. Hence, it is essential to delineate the diabetes-specific mechanisms that accelerate cardiovascular disease to identify the optimal therapeutic regimens to combat these heterogeneous diseases.

Hyperglycemia is both defining and common to types 1 and 2 diabetes, yet there are common and distinct threads in these two syndromes. The potential underlying mechanisms linking diabetes and cardiovascular complications may differ, at least in part, between these two most common forms of diabetes. Specifically, insulin resistance is significantly more common in type 2 diabetes, but it may appear in later stages of type 1 diabetes as well. Furthermore, hyperinsulinemia is more associated with type 2 diabetes, because type 1 diabetes, at least in the absence of therapies, is caused by a reduction in naturally produced and circulating insulin. In this chapter we review the evidence supporting, or not, the roles of hyperglycemia, hyperinsulinemia, and insulin resistance in cardiovascular complications. Note that this chapter does not consider in depth the influences of dyslipidemia, inflammation, hypercoagulability, or endothelial dysfunction in diabetes; these are the focus of **Chapter 10**.

Diabetes and Atherosclerosis: What Is the Role of Hyperglycemia?

Long-term intervention studies have begun to answer the critical question of whether strict control of hyperglycemia imbues protection or at least reduction in cardiovascular consequences in diabetes. The answer to this question may depend on the cause of diabetes.

In type 1 diabetes, reviewed more extensively in **Chapter 11 by Dr. Maahs**, the results of the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study have provided clear answers. In the original DCCT study, type 1 diabetic subjects were adolescents versus young adults at the time of entry into the study. Specifically, of the adolescents, the mean age of subjects randomized to either arm of strict versus standard glycemic control was age 15 years (a total of 87 patients). Of the adults, the mean age of patients randomized to either arm of glycemic control was age 28 years (a total of 191 patients).[2] Strict control of hyperglycemia was shown early in the study to reduce microvascular complications of diabetes compared with standard regimens of glycemic control.[3] However, because of the delay in cardiovascular events in this population, most likely a result of the younger age at entry into the study, the answer to the question of cardiovascular complications was revealed years later and particularly in the follow-up study to the DCCT, the EDIC study. Both surrogate markers of atherosclerosis (carotid intima-media thickness) and myocardial infarction, stroke, and death from cardiovascular consequences were shown to be reduced in the group of patients treated with strict versus standard regiments of glucose control.[4,5] It is important to note that the reduced cardiovascular complications were evident years after the levels of glycosylated hemoglobin between both groups became indistinguishable, suggesting a "legacy" effect. The legacy effect—mechanisms and implications—is discussed later.

In type 2 diabetes, current epidemiologic data have identified that the overall risk of cardiovascular complications is twofold to fourfold greater than that observed in nondiabetic patients, even after accounting for the traditional risk factors. In type 2 diabetes, the heterogeneous nature of the concomitant ailments and exposures, such as hyperlipidemia, hypertension, obesity, smoking, and environmental pollutants, has rendered the question of the specific role of hyperglycemia more difficult to address

unequivocally. The United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetic patients was originally composed of 3867 patients randomized to strict versus standard glycemic control. After 10 years the study showed that levels of glycosylated hemoglobin were significantly lower in the strict control group versus standard (7.0% versus 7.9%, respectively). In parallel, the UKPDS reported a 16% reduction in risk of myocardial infarction, but the result did not achieve statistical significance.[6] Years later, however, in the post-trial monitoring program, even after glycosylated hemoglobin levels were indistinguishable from those in the former standard control group, the risk of myocardial infarction was significantly lower in the former strict glycemic control group.[7] As in the case of type 1 diabetes and the DCCT and EDIC trials, the results of the UKPDS suggested that a legacy effect might have imparted long-term cardiovascular benefit in the group previously treated with strict glycemic control.

It is noteworthy that a recent study, ACCORD (Action to Control Cardiovascular Risk in Diabetes), found that stricter control of glycemia versus standard regimens in type 2 diabetes was associated with higher cardiovascular mortality as well as higher all-cause mortality, leading to premature discontinuation of the glycemic control arms of the study for safety purposes, after a mean follow-up period of 3.5 years. There was, however, a non–statistically significant trend toward lower nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes in those in the glycemic control groups.[8] More recent analysis has suggested that the risk of hypoglycemia was greater in the glycemic control arms and might have contributed to the increased cardiovascular risk. From the multiple analyses of ACCORD and two other related studies—ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)[9] and VADT (Veterans Affairs Diabetes Trial)[10]—in which glycemic control arms in type 2 diabetes were associated with neither reduced nor higher cardiovascular events, refined recommendations for the implementation of glycemic control are emerging, because subgroup analyses may suggest reduction in cardiovascular disease in the glycemic control arms based on entry cardiovascular disease surrogate markers, such as coronary calcification scores. Hence, cardiovascular status at entry into the study may in fact define the groups most likely to benefit, and not be harmed, by glycemic control measures.

In addition to glycemic control measures, the Steno-2 trial showed that a broader approach to management, including glycemic control and control of lipid levels, blood pressure, and microalbuminuria in type 2 diabetic patients led to a 50% reduction in cardiovascular mortality.[11,12] The Steno-2 studies, however, did not identify the specific factor or combination of factors most responsible for cardiovascular benefit.

In the following sections we review the evidence that hyperglycemia and its consequences contribute to atherosclerosis in diabetes.

Polyol Pathway

The two major enzymes of the polyol pathway include aldose reductase (AR), the first and rate-limiting enzyme of this pathway, and sorbitol dehydrogenase (SDH). By the action of these enzymes, glucose is metabolized to sorbitol and fructose, respectively. In the process, as shown later, AR action results in the conversion of nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) to nicotinamide adenine dinucleotide phosphate ($NADP^+$) and the action of SDH consumes nicotinamide adenine dinucleotide (NAD^+) to yield NADH.[13]

Compared with human or rat tissues, in the mouse the levels of AR are significantly lower; hence, a strategy to specifically test the role of AR in atherosclerosis used transgenic mice, which expressed human-relevant levels of AR on the major histocompatibility type 1 promoter, thereby exerting global overexpression of the enzyme. When these mice were bred with mice deficient in the low-density lipoprotein (LDL) receptor and made diabetic with streptozotocin, a significant increase in atherosclerosis, both by percentage of aortic arch lesion area and by en face analysis of the entire aorta, resulted after 6 weeks of a high-cholesterol diet, without a change in total cholesterol or triglyceride or in levels of very low-density lipoprotein cholesterol (VLDL-C), LDL-C, or high-density lipoprotein cholesterol (HDL-C) in the two groups of diabetic mice (those overexpressing or not transgenic for human AR [hAR]) (**Fig. 9-1**).[14] Similar roles for hAR in acceleration of atherosclerosis in diabetic LDL receptor null mice fed a high-cholesterol diet at 8 or 12 weeks were found, and when mice were fed a cholic acid–containing diet, atherosclerosis increased in the diabetic tg hAR animals versus the nondiabetic LDL receptor null mice.[14] Of note, there were no differences observed in nondiabetic mice overexpressing transgenic hAR or not in the LDL receptor null background, thereby suggesting that glucose flux via the polyol pathway was specific to the diabetic state in atherosclerosis. In parallel with increased atherosclerosis in the diabetic transgenic hAR-overexpressing mouse, macrophages retrieved from these animals revealed increased expression of inflammatory mediators and greater uptake of modified lipoproteins. In addition to these findings in mice, Gleissner and colleagues discovered increased expression and activity of AR in human monocyte-derived macrophages during foam cell formation stimulated by oxidized LDL (oxLDL), a process that was further exacerbated when macrophages were grown in hyperglycemic conditions (30 mM D-glucose) compared with osmotic control conditions.[15]

Recent studies by Vedantham and colleagues demonstrated that when tg hAR mice were bred into the apoE null background and rendered diabetic with streptozotocin, increased atherosclerosis ensued compared with the nontransgenic diabetic apoE null mice (see **Fig. 9-1A, B**). As in the case of LDL receptor null mice, there was no effect of transgenic hAR expression in the nondiabetic apoE null mice. Furthermore, they showed that administration of an AR inhibitor, zopolrestat, was effective in reducing accelerated atherosclerosis in the diabetic transgenic hAR mice in the apoE null background (see **Fig. 9-1C**). Important roles for endothelial cell hAR in diabetic atherosclerosis were demonstrated in that work. When tg Tie2-hAR mice in the apolipoprotein (apo) E null background were rendered diabetic with streptozotocin, atherosclerotic lesion size was increased, suggesting that endothelial cell AR contributes importantly to acceleration of atherosclerosis in diabetes.[16]

It is important to note that an earlier study suggested that distinct inhibitors of AR (ARIs; tolrestat and sorbinil) and genetic ablation of AR in diabetic apoE null mice increased early lesion formation as a result of increased levels of toxic aldehydes in the lipid particles.[17] Differences in the mouse models, specifically genetic overexpression of AR to human

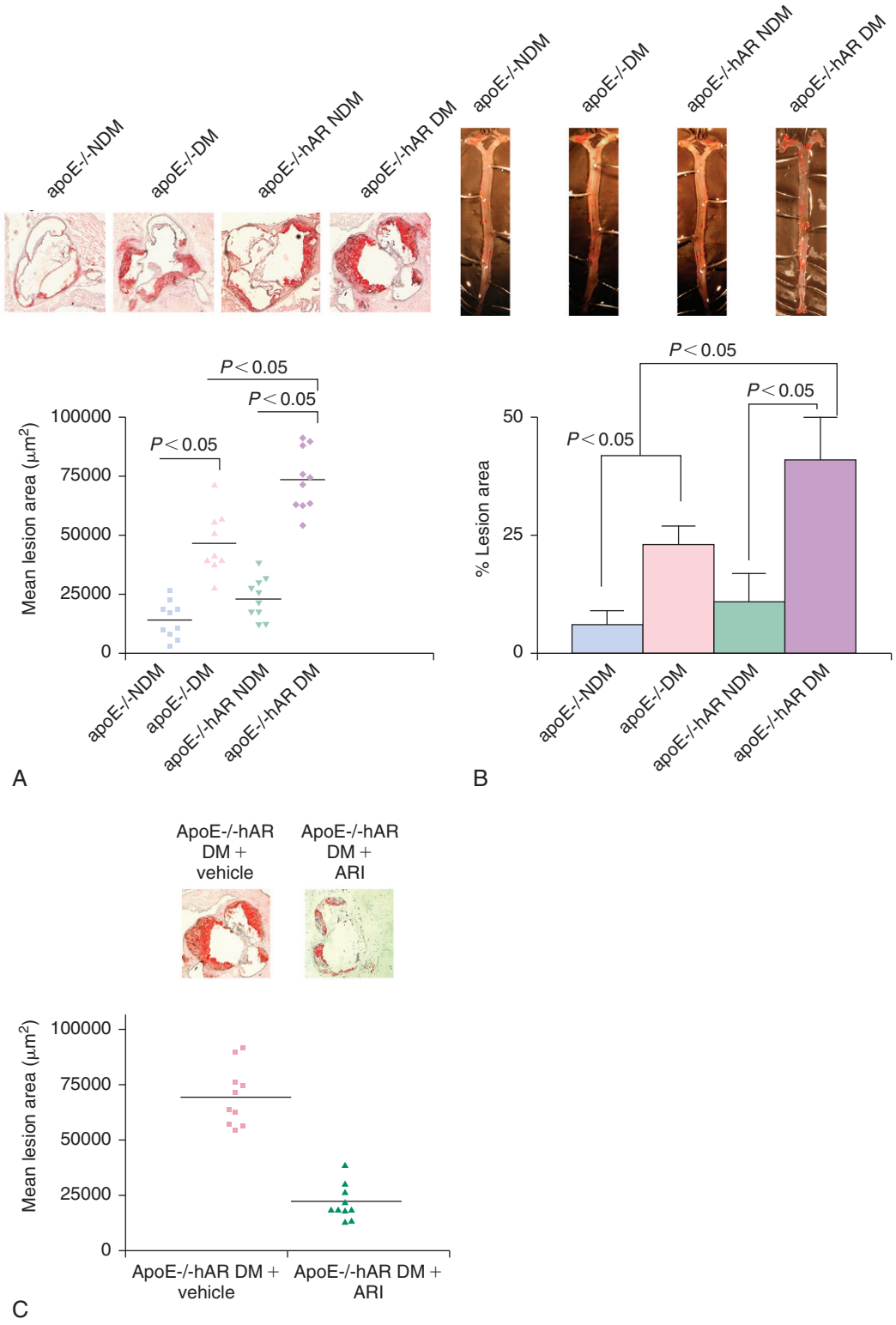


FIGURE 9-1 Impact of diabetes and aldose reductase (AR) expression on atherosclerosis at 14 weeks after induction of diabetes. Shown are representative images of aortic root sections stained with oil red O **(A)** and Sudan IV stained aortic enface **(B).** Hearts were retrieved from nondiabetic and diabetic apoE −/− (n = 10 and 9, respectively) mice, nondiabetic and diabetic apoE −/− hAR + (n = 10 in each group) mice, and diabetic apoE −/− hAR + mice treated with and without aldose reductase inhibitor (ARI) (n = 10 and 10, respectively) **(C)**, and mean atherosclerotic lesion areas were determined. *(Reprinted from Vedantham S, et al., 2012.*[16]*)*

relevant levels or complete genetic deletion, as well as potential distinct off-target effects of the different ARIs may underlie these findings. In human patients with diabetes and neuropathy, however, 1 year of treatment with the ARI zopolrestat resulted in improved cardiac function, not worsened function, as measured by echocardiography.[18] In contrast, the vehicle-treated diabetic patients continued to display reduction in their cardiac function. This study, which did not directly address diabetic atherosclerosis, did however suggest that pharmacologic inhibition of AR by zopolrestat did not worsen cardiovascular complications of diabetes. Hence, it is possible that more potent ARIs with

less off-target effects may hold promise for the treatment of atherosclerosis in diabetes.

Finally, it is important to note that increased oxidative stress may result from the overactivity of the polyol pathway.[19] NADPH is a cofactor of glutathione production; consumption of glutathione by action of the polyol pathway may result in reduced availability of this antioxidant mechanism.[20] These considerations are consistent with the observations in mouse models and human macrophages that AR activity increases oxidative stress on high glucose and oxLDL exposure.

Hexosamine Pathway

When excess levels of glucose are shunted into the hexosamine biosynthetic pathway (HBP), products emerge that have been shown to cause endoplasmic reticulum stress and to alter transcriptional activity of key molecules implicated in atherosclerosis. In this pathway, fructose-6-phosphate is converted to glucosamine-6-phosphate and uridine diphosphate (UDP)–*N*-acetyl glucosamine via the actions of the rate-limiting enzyme of the hexosamine pathway, L-glutamine:D-fructose-6-phosphate amidotransferase (GFAT).[21]

Examples of how the HBP may contribute to conditions that exacerbate atherosclerosis in diabetes include the following. First, in a manner dependent on mitochondrial superoxide production, hyperglycemia increases hexosamine biosynthesis and *O*-glycosylation of the transcription factor Sp1 in bovine aortic endothelial cells. Consequences of increased modification of Sp1 include increased expression of plasminogen activator inhibitor type 1 (PAI-1) and transforming growth factor beta 1 (TGF-β1).[22] Second, findings similar to the effects of high glucose and the HBP on PAI-1 expression were also shown in adipose tissue.[23] Third, in bovine aortic endothelial cells, endothelial nitric oxide synthase (eNOS) activity was inhibited by HBP-mediated increases in *O*-linked *N*-acetylglucosamine modification of eNOS and a decrease in *O*-linked serine phosphorylation at residue 1177.[24] In the aortas of diabetic mice, similar changes in eNOS activity and these post-translational modifications were also observed. Because reduced eNOS activity is observed in diabetes and linked to endothelial dysfunction, HBP-mediated reductions in eNOS activity spurred by hyperglycemia may contribute to endothelial cell dysfunction, which presages accelerated atherosclerosis.

Protein Kinase C

Hyperglycemia stimulates the generation of diacylglycerol (DAG), which is an activator of at least certain isoforms of protein kinase C (PKC).[25] The PKC family of enzymes consists of at least 12 members.[26] PKCs are involved in a diverse array of cellular functions, many of which may be considered to play roles in diabetic atherosclerosis, such as cellular proliferation, signal transduction, cellular fate, and transcription factor modulation (e.g., Egr1, NF-κB, and Sp1), cytokine expression, and oxidative stress in cells such as endothelial cells, smooth muscle cells, and monocytes and macrophages, all of which contribute to atherosclerosis mechanisms.[27]

In atherosclerosis, isoforms of PKC have been implicated in the pathogenesis of this disorder. First, work by Harja and colleagues showed that global deletion of the PKCβ isoform resulted in significant reduction in atherosclerosis in apoE null mice, even without diabetes.[28] In parallel, these researchers showed that a chief mechanism by which deletion of this PKC isoform was protective was by reduction in the vascular expression of the key transcription factor, Egr1. Egr1, previously shown to influence proinflammatory and prothrombotic genes in atherosclerosis, is regulated by PKCβ. Furthermore, treatment of the apoE null mice with the PKCβ inhibitor LY333531 (or ruboxistaurin) resulted in decreased atherosclerosis. This work, although not performed in diabetic animals, nevertheless may suggest that this PKC isoform may play key roles in diabetic atherosclerosis. Supportive of this conclusion is the report showing that administration of ruboxistaurin to type 2 diabetic patients improved brachial artery flow-mediated dilation compared with vehicle treatment.[29] In addition to PKCβ, possible protective roles for PKCδ in atherosclerosis have been suggested, particularly in smooth muscle cell survival. In a model of vein graft atherosclerosis in nondiabetic mice, deletion of PKCδ resulted in more severe atherosclerosis.[30] As in the case of PKCβ, further studies are essential to determine potential implications in diabetes.

Other studies have suggested that advanced glycation endproduct (AGE) pathways may contribute to activation of PKC isoforms—for example, studies reported in bovine retinal endothelial cells.[31]

Oxidative Stress

Studies testing samples retrieved from humans and animals with diabetes show increased levels of markers of oxidative stress such as plasma and urinary F2-isoprostanes and 8-hydroxydeoxyguanosine.[32,33] Such markers of increased oxidative stress have been linked to diabetic complications, and in aortic rings retrieved from type 1 or type 2 diabetic animals, oxidative stress appears to contribute to endothelial dysfunction.[34] Beyond endothelial dysfunction, specific roles for oxidative stress in diabetes were suggested by experiments in which heterozygous deletion of the lipoic acid synthase gene in streptozotocin-induced diabetic apoE null mice resulted in marked increases in atherosclerosis compared with diabetic mice expressing lipoic acid synthase.[35] In the atherosclerotic lesions of the mice with heterozygous deletion of lipoic acid synthase, more macrophages and greater degrees of cellular apoptosis were observed. In addition, oxidative stress and markers of inflammation such as interleukin 6 (IL-6) were observed. These studies directly suggested that oxidative stress was an important contributing mechanism to diabetes-associated accelerated atherosclerosis.

Although antioxidant therapies in the clinic have been generally disappointing, e.g. a large-scale study of the use of vitamin E (400 IU/day) in patients at high risk for cardiovascular disease (such as diabetic patients), it has been suggested that the potency and half-life of available antioxidants may not be consistent with the potential for longstanding protection against diabetic vascular dysfunction.[36] Furthermore, others have suggested that perhaps treatment of the most at-risk patients in terms of exaggerated oxidative stress might be useful, such as those bearing the haptoglobin (Hp) 2-2 genotype.[37] Given the multiple potential caveats regarding the specific antioxidant, dose, schedule, and vulnerable populations in exacting the greatest efficacy from this class of molecules, it is not surprising that the specific sources of oxidative stress in diabetes are a subject of intense investigation.

In diabetes, two major sources of oxidative stress have been suggested by experimental model systems. In the first case, it has been proposed that in endothelial cells, as well in other cell types, hyperglycemia results in overproduction of

mitochondrial reactive oxygen species (ROSs) and that such increases in ROSs relay many adverse consequences in the vasculature, such as activation of PARP (poly [ADP-ribose] polymerase) and endothelial upregulation of an array of prothrombotic and proinflammatory molecules.[38,39] In this context, it has been suggested that such overproduction of mitochondrial ROSs might in fact underlie increased activity of other pathways implicated in diabetic cardiovascular disease, such as activation of the HBP pathway (discussed earlier) and PKC and glycation and activation of the receptor for AGE (RAGE) (see later). Although earlier efforts focused on the use of benfotiamine as a means to reduce the consequences of excess mitochondrial ROS production driven by high glucose,[40] more recent publications suggest that mitochondrially targeted antioxidants are under development to address the issue of availability and sustainability in pathophysiologic settings characterized by deleterious levels of oxidative stress.[41]

In addition to increased mitochondrial sources of ROSs in hyperglycemia and diabetes, ROSs derived from NADPH oxidase have been extensively studied.[42] There are multiple forms of Nox, and conserved among these six-transmembrane domain family members are binding sites for NADPH, flavin adenine dinucleotide (FAD), and two hemes.[43] Nox isoforms may be activated by hyperglycemia as well as by AGE and RAGE pathways.[44] Hence, multiple fuel forward mechanisms initiated by high levels of glucose may generate and sustain ROS production by this family of pro-oxidant molecules.

Using specific Nox-modified animals, it has been shown that deletion of p47phox subunit of the Nox1 and Nox2 complex in apoE null mice (without diabetes) resulted in decreased atherosclerosis in a manner independent of diet or serum lipid levels. Superoxide production in the vessel wall was reduced by this genetic approach, and smooth muscle proliferation was also suppressed.[45] Mice deficient in both Nox1 and apoE demonstrated reduced atherogenesis in parallel with decreased macrophage infiltration in the lesions.[46] Similar findings were observed in nondiabetic Nox2 null mice in the apoE null background fed a high-fat diet. Decreased aortic ROS production was observed in these animals compared with the Nox2-expressing counterpart apoE null mice.[47] Such findings may have implications for the pathogenesis of diabetes-accelerated atherosclerosis, although this has not been formally proved.

Other studies consistent with a key role for oxidative stress in atherosclerosis (nondiabetic) were performed in diabetic LDL receptor mice devoid of glutathione peroxidase. In these animals, increased atherosclerosis and inflammation resulted.[48] Of note, in tg hAR mice in the LDL receptor null background with streptozotocin-induced type 1 diabetes, levels of glutathione peroxidase in the aorta were significantly lower than those observed in the diabetic LDL receptor null mice not expressing hAR.[14] Taken together, these data indicate that loss of key antioxidant protective enzymes in atherosclerosis is deleterious.

Association studies in human aortas suggested that increased expression of Nox4 was found to be decreased in regions of the aorta with de-differentiated smooth muscle cells. In contrast, strong expression of Nox4 was observed in smooth muscle cells within the aorta that retained the contractile phenotype.[49] It is important to note that various classes of compounds are under development for isoform-specific inhibition of Noxes. These advances may need to be viewed with caution, because it is possible that isoform specificity of the inhibitors may not be feasible, and furthermore that ROS production has salutary effects in vivo, such as in responses to infectious challenges.[50] In this context, broad inhibition of Nox isoforms may be accompanied by side effects. Hence, a careful and isoform- and cell-specific strategy may be most beneficial. Until cell-specific deletion of various Nox isoforms in diabetic mice with atherosclerosis or subjected to infections challenge has been performed, the broad applicability of such inhibitors in chronic diseases such as diabetes is an untested concept.

Glycation: Receptor-Dependent and Independent Mechanisms in Diabetic Atherosclerosis

In addition to the multiple direct consequences of high levels of glucose, "indirect" consequences of this metabolic state include the nonenzymatic glycation and oxidation of proteins and lipids to form AGEs.[51] The critical "intermediates" in these pathways to AGE formation are the dicarbonyl compounds, such as methylglyoxal (MG), glyoxal, and 3-deoxyglucone (3-DG) (**Fig. 9-2**). There are multiple mechanisms implicated in the formation of AGEs: (1) reactions between the aldehydic group of reducing sugars with proteins or lipids, forming the Schiff bases and Amadori products; (2) glucose flux via the polyol pathway; and (3) lipid and sugar oxidation steps.[52] These dicarbonyl intermediate products may undergo further rearrangements to generate AGEs. AGEs are a heterogeneous group of compounds and include the highly cross-linked "brown" fluorescent AGEs such as pentosidine and crosslines; the nonfluorescent cross-linking AGEs such as arginine-lysine imidazole; and the non–cross-linking forms of AGEs such as carboxymethyl lysine (CML)–AGEs.[53]

AGEs also form in distinct settings that may exacerbate AGE complications in diabetic tissues. For example, natural aging may lead to AGE formation, particularly on long-lived proteins whose exposure to even normal levels of glucose may gradually lead to the formation of AGEs. Hypoxia and ischemia/reperfusion (I/R) may generate AGEs, thereby increasing AGE damage in settings such as myocardial infarction, stroke, or severe peripheral vascular disease.[54] Renal failure is a setting in which AGE formation is greatly accelerated; in patients with diabetes and severe nephropathy, the accelerated formation of AGEs atop basal diabetes-associated glycation may greatly increase the production and accumulation of these damaging species.[55] In other settings, the actions of the myeloperoxidase enzyme have been shown to generate CML-AGEs.[56] Hence, in infectious or inflamed milieus, the action of inflammatory cell myeloperoxidase in generation of AGEs may lead to further tissues stress, thereby, perhaps, impairing effective wound healing mechanisms.

It has been postulated that food-derived AGEs may form in high-temperature cooking conditions.[57] Other forms of AGE exposure have been suggested in environmental pollutants such as in fly ash particles.[58] Taken together, although AGEs may form in conditions beyond hyperglycemia, it is conceivable that AGE formation in associated conditions, such as those delineated previously, may in fact exacerbate AGE damaging pathways in the diabetic tissues.

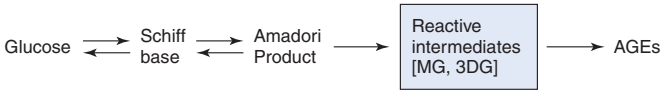


FIGURE 9-2 Mechanisms of hyperglycemia-induced AGE generation.

It is noteworthy that a chief detoxification mechanism for one class of the toxic AGE precursors, the MG dicarbonyl, is the glyoxalase enzyme system or Glo1. Glo1 blocks MG formation into AGEs, resulting in the production of lactate.[59] Glo1 is a glutathione-dependent enzyme. In RAGE-deficient mice, levels of Glo1 mRNA and protein are significantly higher in the kidneys compared with those found in diabetic wild-type RAGE-expressing mice.[60] This may result, in part, because of (1) decreased RAGE-dependent generation of ROSs (which depletes glutathione) and (2) RAGE-dependent transcriptional regulation of Glo1 (**Fig. 9-3**).

Receptor-Independent Pathways

One of the significant consequences of the cross-linking AGEs in particular is the formation of intermolecular bonds between extracellular matrix (ECM) elements. There are multiple potential consequences of such AGE formation in the vasculature such as arterial stiffness and trapping of molecules in the vascular tissues. Trapping of oxidized lipoproteins, for example, may contribute to early atherogenesis mechanisms in the diabetic macrovessels.[61] We and others have shown that oxLDL contains significant degrees of AGE.[62] Furthermore, AGE-induced modification of the ECM in the microvessels or macrovessels may result in increased vascular permeability, thereby facilitating the movement of inflammatory or other cells into the perturbed vessel wall.[63]

Receptor-Dependent Pathways

Given the heterogeneous nature of the AGEs, it is not surprising that multiple different AGE "receptors" have been identified, such as AGE-R1 (an anti-inflammatory AGE receptor),[64] members of the scavenger receptor families such as CD36,[65] and the macrophage scavenger receptor.[66] Among the AGE receptors, the receptor for AGEs (RAGE) is a well-characterized signal transduction receptor of the immunoglobulin superfamily.[67] RAGE binds AGEs such as CML-AGE and possibly hydroimidazolone AGEs.[68] Very likely, distinct AGEs may bind to RAGE as well.

RAGE is characterized by the presence of three extracellular domains led by an *N*-terminal V-type Ig domain. This is followed by two distinct C-type Ig domains.[69] A number of recent publications have implicated the V-C1 domain as a chief unit for ligand binding.[70] Two recent papers reporting on the structure of extracellular RAGE indicated that it is composed of a large hydrophobic patch and a large negative patch; these regions modulate the patterns of RAGE ligand binding profiles to this region.[71,72]

In addition to AGEs, RAGE also binds distinct ligands. RAGE is a signal transduction receptor for at least certain of the S100/calgranulin family members.[73] Although RAGE was first described as a receptor for S100A12, distinct work has shown that S100B, S100P, S100A8/A9, S100A4, and S100A6, as examples, may bind to and signal via RAGE.[70] Members of the S100 family exert multiple effects in the tissues, including induction and sustenance of inflammatory reactions, and in tumors, S100s are linked to tumor cell proliferation, migration, upregulation of matrix metalloproteinase expression and activity, and the regulation of cell survival.[74] RAGE is also a signal transducer for high-mobility group box 1 (HMGB1).[75] HMGB1, like many of the RAGE ligand families, is also promiscuous and is able to bind to not only RAGE but also certain members of the toll receptor signaling family.[76] Like S100/calgranulins, HMGB1 exerts both proinflammatory and protumor properties. In tumor cells, HMGB1 has been suggested to mediate, via RAGE, increased pancreatic tumor cell autophagy and decreased apoptosis, processes that together enhance tumor cell survival.[77] RAGE is also a receptor for amyloid-β peptide and other forms of amyloidogenic polypeptides.[78] Recent work has shown that RAGE binds complement-related factor C1q[79] and that RAGE is a signaling receptor for lysophosphatidic acid (LPA).[80] Hence, these considerations highlight the complexity of RAGE; RAGE is not simply a "one ligand–one disease" molecule. Rather, we speculate that multiple ligands of RAGE may converge in distinct settings and thereby contribute, perhaps at different time points, to the pathogenesis of chronic diseases such as diabetic atherosclerosis. Taken together, the multi-ligand nature of RAGE places this molecule in the midst of cellular milieus in which hyperglycemia, inflammation, and tumor propagation are key events. A plethora of evidence links these ligands to diabetes and atherosclerosis in humans and in animal models.

In that context, one of the first tests of RAGE in human diabetic atherosclerosis was its expression pattern in the affected tissues. Human atherosclerotic plaques subjected to immunohistochemical localization of RAGE demonstrated that RAGE was expressed in atherosclerotic plaques retrieved at carotid endarterectomy[81] and in coronary artery lesions[82] but to greater degrees in the lesions retrieved from the diabetic versus nondiabetic patients. In these settings, RAGE expression in the diabetic lesions was associated with greater degrees of inflammation (higher numbers of macrophages and T cells), increased activation of NF-κB and expression of COX-2/mPGES-1, increased expression and activity of matrix metalloproteinase (MMPs), higher numbers of apoptotic smooth muscle cells, and higher levels of the RAGE ligand S100A12. It is interesting to note that RAGE expression in the diabetic carotid plaques increased in parallel with the levels of glycosylated hemoglobin. Indeed, at the level of the RAGE *(AGER)* gene, RAGE ligands such as AGEs contribute to upregulation of RAGE itself, at least in part via NF-κB binding elements within the RAGE promoter.[83]

RAGE is expressed in multiple cell types linked to atherosclerosis, such as endothelial cells, monocytes and macrophages, smooth muscle cells, and T lymphocytes. In these cell types, RAGE ligands have been shown to mediate upregulation of inflammatory signals and key transcription factors such as NF-κB and Egr-1 that have been shown to contribute critically to atherosclerosis, including that in diabetes.[84]

In vivo studies have used a variety of approaches to test the role of RAGE in diabetic atherosclerosis in animal models. Mice deficient in apoE made type 1 diabetic with streptozotocin demonstrated increased atherosclerotic plaque area at the aortic sinus and increased vascular inflammation compared with vehicle-treated mice whose levels of glucose were within the normal range. The role of RAGE was initially tested

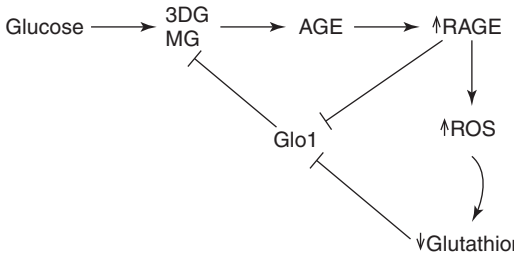


FIGURE 9-3 **Methylglyoxal and glyoxalase1: influence of RAGE and ROSs.**

with use of soluble RAGE (sRAGE), the extracellular ligand-binding domain of RAGE. Administration of sRAGE to diabetic apoE null mice resulted in a dose-dependent suppression of early acceleration of atherosclerosis and, in other studies, suppression of progression of accelerated diabetic atherosclerosis.[85,86] Of note, although levels of cholesterol were higher in the streptozotocin-treated mice, administration of sRAGE had no effect on levels of cholesterol in the diabetic animals. Rather, administration of sRAGE reduced inflammation in the aorta tissue—even tissue not directly affected by vascular lesions. Similar findings were observed in type 2 diabetic mice (db/db) in the apoE null background; administration of sRAGE reduced atherosclerosis.[87]

In additional approaches, mice globally devoid of RAGE or mice in which endothelial cell signaling was impaired by virtue of deletion of the RAGE cytoplasmic domain in endothelial cells (and other cell types in which preproendothelin-1 promoter might have been active) demonstrated significant reduction in atherosclerosis, including that in diabetes, in a manner independent of cholesterol or lipid levels.[62,88] Affymetrix gene array studies highlighted roles for the ROCK1 branch of the TGF-β signaling pathway in smooth muscle cells in regulation of migration and proliferation.[89]

Recent studies have uncovered that the cytoplasmic domain of RAGE binds to the formin family molecule diaphanous-1 (mDia1). The formins are a family of molecules that contribute to regulation of cellular signaling (effectors of Rho GTPase molecules) and to cellular migration and cytokinesis.[90] Studies to date in transformed cells, smooth muscle cells, and macrophages have illustrated that RAGE ligand-dependent signaling in these cell types is blocked in the presence of siRNA-knockdown of mDia1 or in mDia1 null cells.[91–93] In vivo, nondiabetic mice subjected to guidewire-induced femoral artery endothelial injury displayed significant upregulation of mDia1, especially in smooth muscle cells (**Fig. 9-4A-I**). Furthermore, mice devoid of mDia1 were protected from aberrant neointimal expansion (**Fig. 9-4J**). Consistent with the concept that mDia1 transduced RAGE signaling in the smooth muscle cells, mDia1 null injured vessels and isolated aortic smooth muscle displayed reduced oxidative stress, cell signaling via GSK-3β, and cellular migration compared with wild-type counterparts expressing mDia1 (**Fig. 9-5**).[92] Prompted by these findings, studies are under way to determine the impact of mDia1 in diabetic atherosclerosis.

Although RAGE antagonists have not yet been tested in humans with diabetic atherosclerosis, evidence is accruing linking RAGE to this disorder. Single-nucleotide polymorphisms (SNPs) of RAGE have been associated with human diabetic atherosclerosis.[94,95] Multiple reports have now described relationships between levels of sRAGE and diabetic cardiovascular disease in humans.[96,97] Hence, in addition to the potential of RAGE as a target for therapeutic intervention in diabetic atherosclerosis, RAGE may also present new biomarker opportunities to track the presence and/or extent of this complication.

It is important to note that RAGE-dependent roles in diabetic atherosclerosis are also accounted for by inflammatory mechanisms in addition to the effect of glycation. Given that multiple RAGE ligands are expressed in diabetic macrovessels and that they largely converge on this specific receptor, it is difficult to precisely discern the effects of individual ligand classes. Hence, targeting this pathway for clinical translation will depend on the identification of RAGE inhibitors. **Chapter 10** presents an in-depth discussion of the broader roles of inflammation in diabetic atherosclerosis.

Additional Mechanisms of Diabetic Atherosclerosis

Recent studies have suggested the certain microRNAs may contribute to regulation of inflammatory pathways in cell

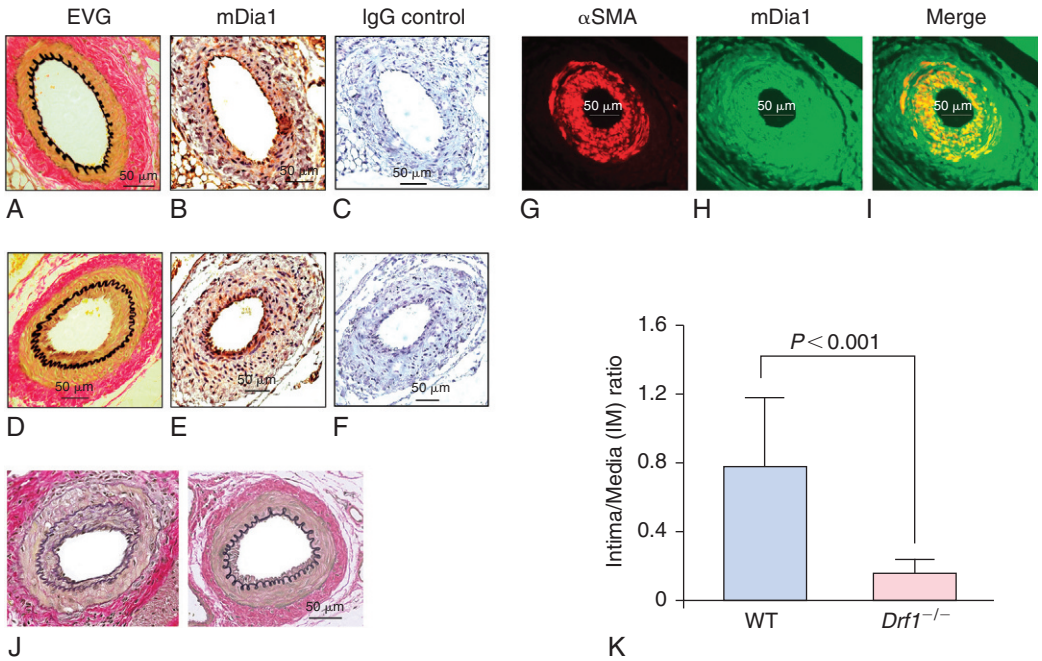


FIGURE 9-4 Increased expression and impact of mDia1 after endothelial denudation injury. Wild-type (WT), *Drf1−/−*, and *RAGE−/−* mice were subjected to femoral artery endothelial denudation or sham, and tissues analyzed at the indicated times. **A** and **D,** Assessment of neointimal expansion by elastic–van Gieson (E-VG) staining on day 21 after injury in WT mice (**A,** sham and **D,** injury). **B, C, E,** and **F,** Immunostaining for mDia1 or isotype IgG control in WT mice on day 21 after injury (**E** and **F**) or sham (**B** and **C**). **G** to **J,** Colocalization studies: sections of injured vessels were stained for mDia1 and α–smooth muscle cell actin (SMA). Immunofluorescence studies revealed a colocalization of the two molecules in the neointima on day 21. **K,** Intima/Media (I/M) ratio measurement based on morphometric analysis of the vessels of WT and aged-sex-matched *Drf1−/−* mice (n = 11/group) was performed 21 days after guidewire-induced femoral artery denudation. Representative images are shown. [92] $P < 0.001$. *(Reprinted from Toure, et al., 2012.)*

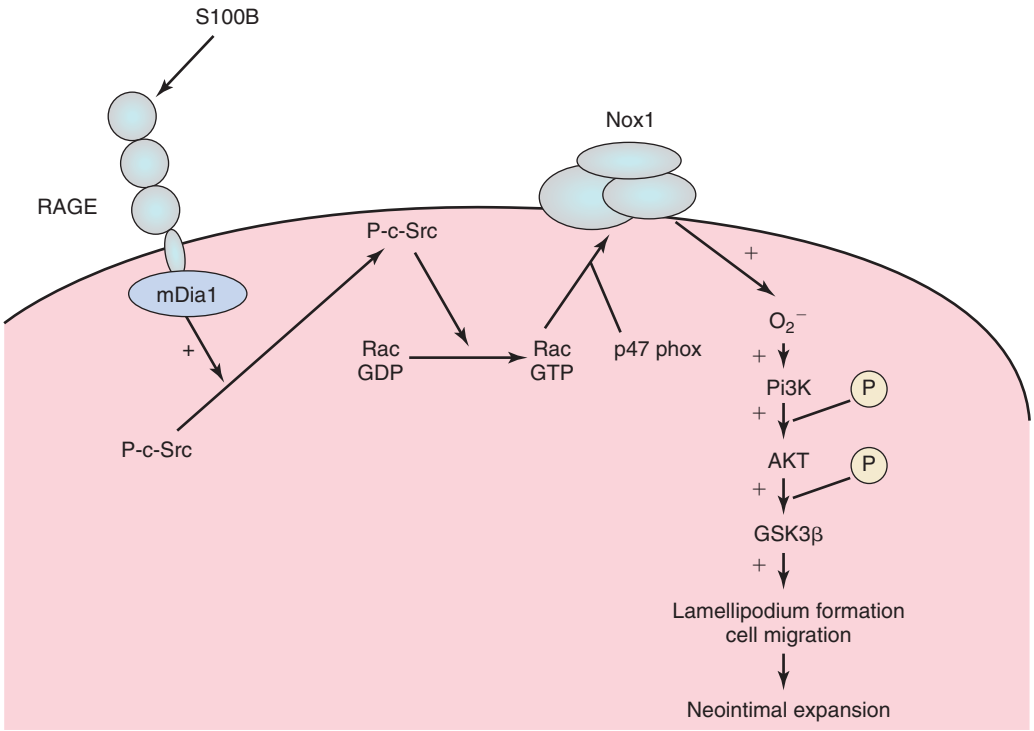


FIGURE 9-5 Proposed mechanism of the role of mDia1 in RAGE-induced redox signaling SMC migration and neointimal expansion. We propose that there is a critical role for mDia1 in transducing the effects of RAGE ligands on P-c-Src, Rac1, and Nox1 activation in consequent phosphorylation of AKT/GSK3β ser 9, processes essential for RAGE ligand-induced vascular SMC migration.[92] *(Reprinted from Toure, et al., 2012.)*

types that mediate diabetic atherosclerosis.[98] For example, miRNA (miR)-16 has been linked to RNA stability of cyclooxygenase (COX-2) in monocytes, and the RAGE ligand S100B downregulates miR-16 levels in these cells.[99] In vascular smooth muscle cells retrieved from type 2 diabetic db/db mice, miR-125 levels were higher than those in nondiabetic control animals. In those cells, higher levels of miR-125 were linked to increased expression of proinflammatory genes such as IL-6 and MCP-1, both key factors that are expressed early in diabetic atherosclerotic lesions in mouse models.[100] In these same smooth muscle cells, it has also been shown that miR-200b levels were higher in the diabetic versus nondiabetic cells and that miR-200b inhibited Zeb1, a factor that negatively regulates inflammatory genes.[101] How such differences in miRs may be directly implicated in diabetic atherosclerosis in vivo will be a key topic for study.

Chromatin-based epigenetic mechanisms have been implicated in the phenomenon of "metabolic memory." Metabolic memory has been suggested to contribute to the so-called "legacy effect" observed in human diabetic patients. As discussed earlier in this chapter, these legacy patients continued to experience benefit from microvascular and macrovascular complications through their earlier strict control of glycemia regimens compared with their counterparts' standard treatment regimens, even years after the original study was completed. Evidence is accruing to link diabetes-associated histone methylation and histone acetylation patterns to gene expression changes that may contribute to macrovascular disease.[102,103] In diabetic conditions, histone acetyltransferases (HATs) and histone deacetylases (HDACs) have been shown to play roles in regulation of inflammatory and oxidative stress genes, and in the NF-κB signaling pathway (another mechanism that has potential to broadly activate proinflammatory pathways). In the case of methylation, ChIP-on-chip studies showed that when monocytes were cultured in high- (diabetes-relevant) versus low-glucose (non–diabetes-relevant) conditions, significant changes in H3K4me-2 activation marks and H3K9me2 repressive marks were observed, thereby suggesting that exposure of these inflammatory cells to high glucose might impart highly significant changes in gene expression programs that might influence diabetic vasculature.

Protective roles for SIRT1 (NAD-dependent histone deacetylase) have been shown in endothelial cells grown in high glucose. In high-glucose–exposed endothelial cells, expression of SIRT1 was found to be decreased. SIRT1 has been linked mechanistically to p53 levels; when levels of SIRT1 were decreased in endothelial cells by high glucose, the acetylation of p53 increased, thereby increasing its activity.[104] In this setting, evidence of high-glucose–induced endothelial senescence was observed but was prevented by overexpression of SIRT1 or by disruption of p53. Hence, as endothelial dysfunction is thought to critically underlie diabetic atherosclerosis, it is highly plausible that the effects of glucose in endothelial cells cause profound derangements in post-translational modifications, thereby providing a mechanism for inflammation, oxidative stress, and upregulation of proatherogenic pathways.

Taken together, multiple mechanisms converge in diabetic macrovessels to create an environment conducive to acceleration of atherosclerosis. Because there is a plethora of evidence that in nondiseased settings, cellular and metabolic pathways play important roles in ongoing vascular repair, it is logical to consider the situation in the diabetic tissues.

Diabetes and Impaired Regression of Atherosclerosis

As medical interventions in the treatment of atherosclerosis have improved, a critical question has been to what extent

patients with diabetes display differences in response to treatments compared with nondiabetic individuals? In the COSMOS study (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects), plaque regression was significantly less in diabetic patients with glycosylated hemoglobin levels exceeding 6.5% compared with patients with more superior glycemic control—despite equivalent reductions in lipid levels.[105] Furthermore, the data analysis from COSMOS revealed that baseline levels of glycosylated hemoglobin were associated with the change in plaque volume. Such data suggest that lipid-related risk factors were not responsible for the differences in plaque responses, but, rather, that factors related to hyperglycemia and its consequences were more likely to reflect the diminished benefit observed in the diabetic patients.

Indeed, experiments in mouse models of atherosclerosis showed that when diabetic and nondiabetic mice were subjected to equivalent degrees of lipid lowering, diabetic animals displayed significantly less regression of established atherosclerosis.[106] When the atherosclerotic lesions of the diabetic mice after normalization of lipid levels were examined more closely, they revealed more macrophages per lesion area compared with the nondiabetic mice, suggesting that macrophage egress from the lesions was reduced. More oxidative stress and higher levels of macrophage M1 versus M2 polarization markers were observed in the diabetic versus nondiabetic lesions.

In addition to impaired regression of diabetic atherosclerosis, additional potential mechanisms linked to vascular injury in diabetes include impaired endothelial repair. Multiple studies have suggested that endothelial progenitor cells (EPCs) were reduced and/or defective in humans with type 1 and type 2 diabetes.[107] Similar findings were observed in diabetic animal models. In db/db mice, it was shown that EPCs were more sensitive to the effects of hypoxia and oxidative stress than nondiabetic control EPCs, in parallel with reduced ability to promote vascularization, diminished migration, and reduced expression of vascular endothelial growth factor (VEGF) and eNOS.[108] In streptozotocin-treated diabetic mice, EPCs were shown to display reduced mobilization and expression of eNOS, as well as reduced responses to stromal derived factor (SDF) and VEGF.[109]

Taken together, substantial evidence supports that multiple potential mechanisms contribute to accelerated diabetic atherosclerosis in humans. Furthermore, the contribution of defective repair mechanisms is important to consider, and endothelial progenitor dysfunction may contribute to the impaired regression of atherosclerosis observed in diabetes despite reduction in levels of lipids.

In the sections to follow, we consider the roles of insulin resistance and hyperinsulinemia on acceleration of atherosclerosis.

INSULIN RESISTANCE, HYPERINSULINEMIA, AND ACCELERATED ATHEROSCLEROSIS

Scope and Complexity of the Problem

Insulin resistance is a defining characteristic of type 2 diabetes, but it exists within a collection of associated disorders, such as hypertension, obesity, and dyslipidemia, each of which independently has been linked to cardiovascular disease.[110] As discussed earlier, a plethora of evidence links type 2 diabetes to cardiovascular complications. The San Antonio Heart Study showed that insulin resistance (as assessed in the patients by homeostatic model assessment, insulin resistance [HOMA-IR]) predicted future cardiovascular disease events.[111] Hence, efforts to understand the discrete role of insulin resistance in the acceleration of atherosclerosis have relied on both epidemiologic data and basic research experimentation. In the sections to follow, we detail the studies that sought to establish potential links among insulin resistance, hyperinsulinemia, and atherosclerosis. Of note, in the literature, "insulin resistance" may refer to the suppression of responsiveness to insulin action (signal transduction) and/or to the effects of hyperinsulinemia.

What Are the Roles of Insulin Resistance and Hyperinsulinemia in Atherosclerosis?

A review of the components of the insulin signaling suggests key roles for the PI3K/Akt signaling pathway as a central intermediary step that leads to the activation of downstream effectors.[112] These downstream effectors, such as phosphorylated FoxO and GSK-3β, may modulate the cellular responsiveness to insulin action and affect the vasculature.[113] The other "arm" of the insulin signaling pathway involves activation of MAP kinases; evidence suggests that in certain cell types insulin resistance selectively affects distinct arms of the pathways.[112] To test these concepts, particularly in the context of cell-specific contributions to insulin signaling and how this might affect organisms overall, insulin signaling in atherosclerosis has been addressed, to date, by the use of tissue-targeted knockout of the insulin receptor (IR) in mice with Cre-loxP technology and by bone marrow transplantation strategies.

Endothelial Cells and Insulin Receptor Signaling

First, we consider the effects of insulin signaling in endothelial cells. The floxed IR mouse has been one of the major tools used in these efforts. In endothelial cells, selective deletion of the IR in atherosclerosis-prone apoE null mice fed normal rodent chow for 24 or 52 weeks resulted in a significant increase in atherosclerosis compared with apoE null mice with IR expression in these cells.[114] There were no differences in levels of plasma glucose, lipids, or insulin or blood pressure in these mice, suggesting that innate, vessel-specific consequences of IR deletion in endothelial cells accounted for these findings. Insights into the potential mechanisms of increased atherosclerosis were deduced by reduced Ser1177 eNOS phosphorylation in the endothelial cell IR null mice together with increased adherence of leukocytes to these endothelial cells via intravital microscopy studies. Increased endothelial cell expression of vascular cell adhesion molecule 1 (VCAM-1) accompanied the deletion of IR in endothelial cells, thereby providing a well-established mechanism for the adherence of leukocytes to vascular structures, a key event in early atherogenesis.

Global deficiency of Akt1 in apoE null mice fed a high-fat Western type diet resulted in highly significant increases in atherosclerosis and more plaque vulnerability, with decreased Ser1177 eNOS phosphorylation in the lesions.[115] Of note, the specific effect of endothelial cell Akt1 in vivo was not discernible from these studies, given that the deletion of Akt1 was global in nature. However, endothelial cells retrieved from mice displayed reduced viability and proliferation. Taken together, these findings strongly support key adaptive roles for endothelial cell IR signaling in regulation of eNOS activity and suppression of vascular inflammation.

Vascular Smooth Muscle Cells and Insulin Receptor Signaling

In vascular smooth muscle cells, heterodimers of IRs and insulin-like growth factor receptors (IGF1Rs) are formed. Experimental evidence suggests that the IGF1 component mostly mediates the effects of insulin in this cell type.[116] IR null vascular smooth muscle cells were incubated with insulin; this resulted in reduced Akt phosphorylation and increased ERK1/2 phosphorylation. Functional responses included an increase in proliferation and migration, likely through the actions of IGF1R.[117] In the work of Fernandez Hernando referred to earlier, smooth muscle cells retrieved from the Akt null mice displayed reduced proliferation and migration, and higher degrees of apoptosis—features that, depending on the stage of atherosclerosis (early or late), might increase plaque vulnerability and atherosclerosis.[115]

Macrophages and Insulin Receptor Signaling

Studies have also been performed testing the role of macrophage IR with both LysM-cre recombinase mice (targeting macrophages, neutrophils, and to some degree monocytes) as well as bone marrow transplantation strategies. It is interesting to note that when these mice were bred with IR-floxed mice into the apoE null background and fed a high-cholesterol, cholate-containing diet, a 50% reduction in en face atherosclerosis resulted, without any differences in lipids or glucose levels.[118] In the macrophages from these animals, responses to LPS or IL-6 were decreased. These data suggested that macrophage IR signaling contributed to inflammation and insulin resistance.

In other studies in apoE null mice devoid of Akt1, more apoptotic macrophages in the lesions were found compared with their Akt1-expressing controls, with no apparent difference in atherosclerosis at the aortic root. The complexity of the implications of macrophage apoptosis in atherosclerotic lesions lies within the context that macrophage apoptosis in late-stage atherosclerotic plaques might contribute to plaque necrosis.[119] Overall, the full scope of implications of macrophage IR signaling in atherosclerosis is yet to be fully delineated for the following reasons related to study design, to date: the degree of macrophage apoptosis in the lesions, the timing of the sacrifice (early versus late atherosclerosis), the type of diet and the degree to which inflammatory substances might skew macrophage-dependent responses (such as the inclusion of cholate), the genetic background of the animals, and the study design (bone marrow transplantation versus LysM-cre recombinase animals). In the last case, the full range of target cells devoid of the IR differ slightly between the two strategies. Additional considerations include whether or not lethal irradiation was first imposed on the animals in the former strategy and the (unknown) extent to which IR signaling might contribute to survival and macrophage properties in that setting.

We may deduce from these data that IR signaling and its role in atherogenesis is dependent on cell type and time course. Finally, we address a recent study that directly tested the role of hyperinsulinemia in atherosclerosis.

The Effect of Hyperinsulinemia on Atherosclerosis

As discussed earlier, in experiments in which insulin resistance is assessed in the context of other distinct and atherosclerosis-stimulating factors, the specific effect of hyperinsulinemia itself on atherosclerosis is difficult to fully dissect. Toward that end, apoE null mice with a single allele deletion of the IR were studied, and the findings were compared with those in apoE null mice with both IR alleles intact. Plasma levels of insulin in the former group of mice were approximately 50% higher than those in the latter group in the fasted state, and 69% higher during a glucose tolerance test (overall, however, glucose tolerance was not different between the two groups of mice). Levels of C-peptide, insulin sensitivity, and postreceptor insulin signaling in muscle, liver, fat, and aorta did not differ between the two groups of animals, nor did levels of plasma lipids or glucose. At two different time courses in these mice fed a normal chow diet, aortic lesion area by en face analysis and at the aortic root did not differ at 24 and 52 weeks of age. Furthermore, cholesterol abundance in the brachiocephalic artery did not differ between the two groups of mice.[120] These data were the first to show that high levels of insulin, without concomitant associated factors that themselves are risk factors for atherosclerosis, exerted no differential effect on atherosclerosis. In that study, however, it is important to note that the animals within these colonies were largely in the C57BL/6 background. The authors reported in the manuscript that the study mice were 87.6% in the C57BL/6 background, as determined by an array that genotyped 377 SNPs in these animals. If and how such a consideration might have affected the conclusions is not possible to determine from the study as designed.

SUMMARY

The worldwide increase in types 1 and 2 diabetes suggests that complications from cardiovascular disease are likely to emerge as leading causes of disability and death in the years to come. Together with the lack of mechanism-based diabetes-specific therapies to combat the disorder, current approaches are limited to treating all of the confounding factors, such as hypertension, hyperlipidemia, and obesity. A number of key studies in type 2 diabetes have failed to show unequivocal benefit of strict glycemic control in reduction of myocardial infarction and death from cardiac events. In type 1 diabetes, the long-term results of DCCT and EDIC did show reduction in both surrogate markers of atherosclerosis, as well as myocardial infarction events and death, with institution of strict glycemic control measures years before the actual occurrence of the cardiac events.

Glucose and its direct and indirect consequences exert profound impact in the cell types highly implicated in atherosclerosis, such as endothelial cells, smooth muscle cells, and macrophages. Of note, the diabetes-specific mechanisms in these distinct cell types may vary according to the time course—that is, mechanisms underlying early lesion initiation may be somewhat different from mechanisms of late-stage lesion progression and plaque instability (**Fig. 9-6**). From this figure, it is apparent that multiple potential therapeutic targets have been identified, based on the results of many years of experimentation on the causes of diabetic accelerated atherosclerosis. We propose that what is needed is a multipronged approach that includes both treatment of comorbid risk factors and mechanism-based therapies that specifically target high glucose and its consequences. Identifying the optimal timing and duration of each therapeutic strategy in diabetic atherosclerosis may be the key to optimal success in treatment of this disorder.

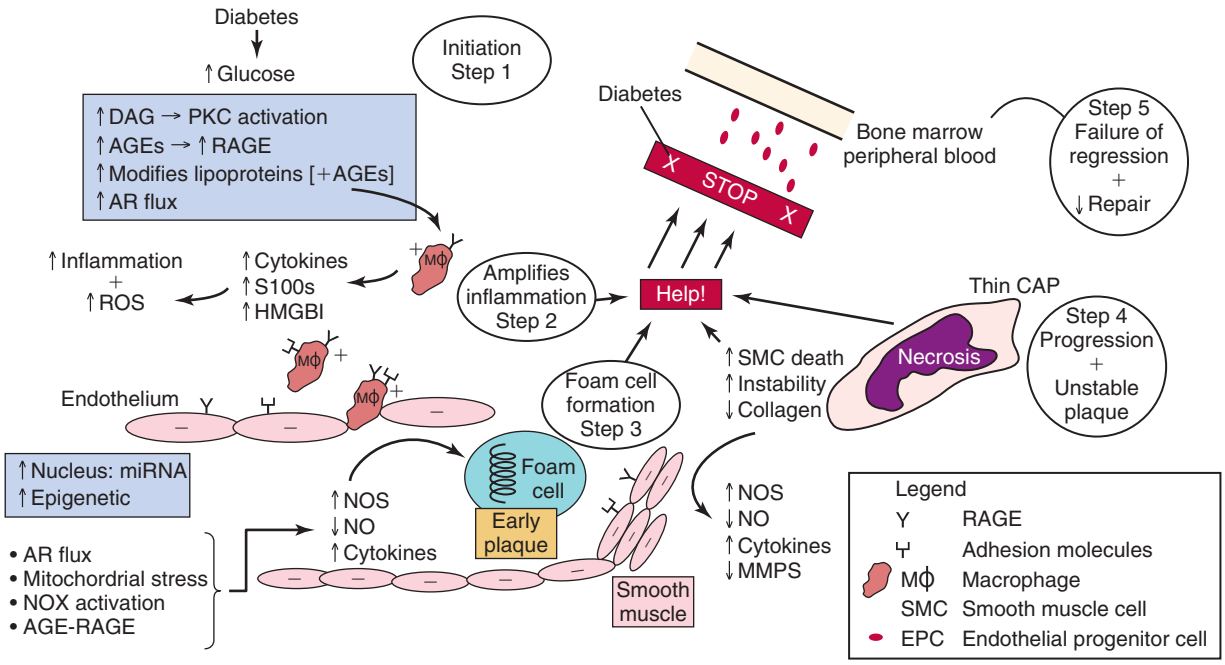


FIGURE 9-6 Mechanisms linked to early initiation versus late progression of diabetic atherosclerotic plaques. Diabetes is characterized by increased levels of glucose. Glucose has multiple consequences, such as increased generation of DAG and activation of PKCs; increased flux via the polyol pathway, which consumes NAD^+, thereby leading to increased fructose, increased AGE precursors, and oxidative stress; increased activation of the hexosamine biosynthetic pathway and concomitant changes in gene expression; increased glycation and post-translational modifications of proteins and lipids that activate RAGE; and increased accumulation of modified lipoproteins, including modification by AGEs *(Initiation, Step 1)*. In this highly proinflammatory environment, macrophages are activated; we predict that such activation of macrophages generates even further inflammation and oxidative stress, in part by release of cytokines, S100/calgranulins, and HMGB1 *(Amplifies inflammation, Step 2)*. Once activated macrophages traverse the activated endothelial cell surface, upregulation of adhesion molecules and inflammatory species increases foam cell formation and the development of the early foam cell *(Foam cell formation, Step 3)*. As smooth muscle cells begin to proliferate and migration, their role is to form stable fibrous caps that protect the plaque from rupture. In late-stage lesions, we hypothesize that smooth muscle cells are more prone to cell death; are more unstable, and produce less collagen and more MMPs *(Progression and unstable plaque, Step 4)*. Finally, published data support that vascular repair mechanisms and atherosclerosis regression are impaired in diabetes. Such dysfunction of repair mechanisms likely forestalls normal vascular maintenance functions and perpetuating atherosclerosis *(Failure of regression and decreased repair, Step 5)*.

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10 Vascular Biology of Atherosclerosis in Patients with Diabetes

Dyslipidemia, Hypercoagulability, Endothelial Dysfunction, and Inflammation

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OVERVIEW

The interaction between diabetes and atherosclerosis is complex and multifactorial. Despite unequivocal evidence for increased cardiovascular disease (CVD) risk in patients with diabetes; a well-documented epidemic of obesity and diabetes; intensive research efforts that include major preclinical scientific progress using unbiased "-omic" approaches; large cardiovascular (CV) outcome studies in diabetes; and new glucose-lowering therapies, the mechanisms that link diabetes to atherosclerosis remain murky. Indeed, challenges in this area begin with simple issues regarding definitions and expand quickly into problems of epistemology. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) differ fundamentally in their root causes, but share increased risk of micro-CVD and macro-CVD as compared with nondiabetic patients. Although these diseases are defined clinically by hyperglycemia, the pathologic picture of T2DM extends beyond glucose. Indeed, recent clinical trial data raise questions regarding whether glucose should be the primary therapeutic target for improving CVD outcomes. Such issues force consideration of other factors in the vascular biology of diabetic atherosclerosis that are outside the glucose-insulin axis discussed in Chapters 1–3.

Although it remains unlikely that one single pathway accounts for how diabetes promotes atherogenesis, atherosclerosis, and atherothrombotic complications, various mediators and pathogenic forces have been uncovered that help explain how the diabetic and even the prediabetic state modulate vascular biology, including specific responses in different cell types (**Fig. 10-1**). Aside from changes in glucose, diabetes is typically characterized by a dyslipidemia involving elevated triglycerides (TGs), lower high-density lipoprotein (HDL) levels, and a low-density lipoprotein (LDL) particle that is more atherogenic.[1–3] Diabetic atherosclerosis involves a prothrombotic state, suggesting basic changes in the coagulation system and its players. Although all cellular components of the arterial wall and the inflammatory system appear involved in diabetic atherosclerosis, the endothelium and its functional roles have been especially implicated in the natural history of T2DM. Inflammation has arisen as a potential central driver in the pathogenesis of diabetes, atherosclerosis, and their intersection. The breadth of abnormalities, whether molecular or clinical, proposed to play a part in T2DM and atherosclerosis independent of glucose is impressive and beyond the scope of any one summary, especially given ongoing rapid evolution in this area. Here we review key concepts regarding how dyslipidemia, hypercoagulability, endothelial dysfunction, and inflammation alter cellular responses that promote atherosclerosis in the setting of diabetes, with an emphasis on emerging concepts, novel targets, and clinical relevance.

DIABETIC DYSLIPIDEMIA

Type 2 diabetes is characterized by a distinct lipid profile involving LDL cholesterol (LDL-C) levels that are often not particularly elevated, higher TG values, and lower HDL cholesterol (HDL-C) concentrations.[2] Also associated with diabetic dyslipidemia are elevated levels of circulating free fatty acids (FFAs). Often this constellation of lipid abnormalities arises early in T2DM including in prediabetic states, drawing further attention to diabetic dyslipidemia as a contributor to the pathogenesis of diabetic atherosclerosis and its complications.[4] Multiple inputs appear to foster diabetic dyslipidemia. Central adiposity may promote dyslipidemia, including the development of secondary factors such as increased inflammation within the fat, systemically, as well as through higher levels of FFAs.[4] The hypertriglyceridemia of diabetes involves changes in both production and combustion: the hepatic secretion of TG-rich lipoproteins such as very low-density lipoproteins (VLDLs) and altered hydrolysis of these and other TG-rich lipoproteins.[5,6] Yet another potential component of hypertriglyceridemia may

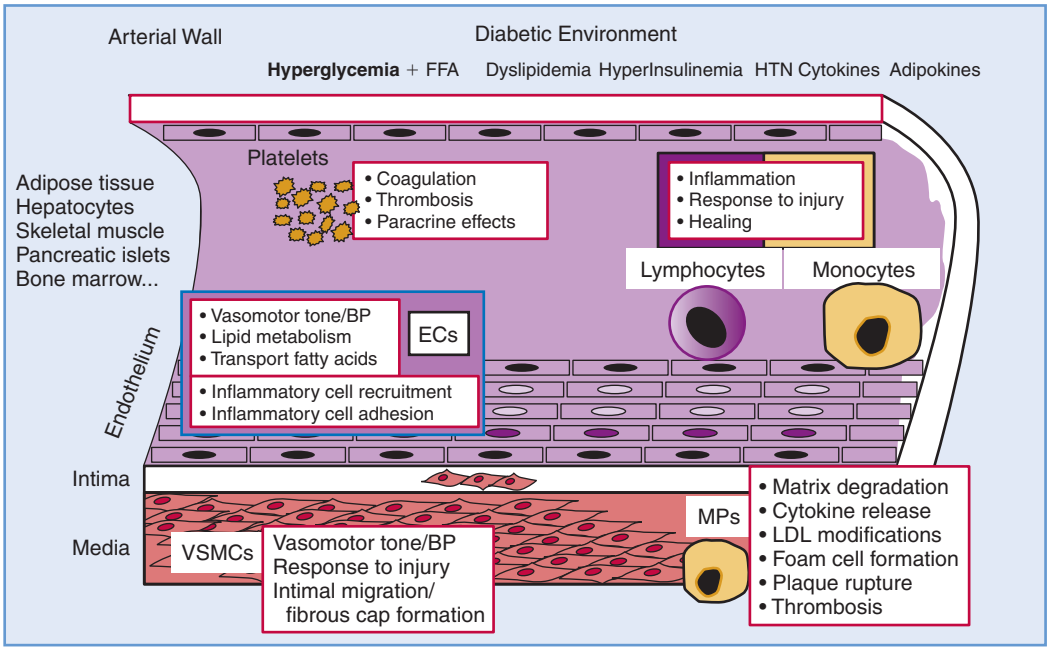


FIGURE 10-1 The arterial wall in diabetes. Although diabetes is defined by hyperglycemia, the key cellular players in the vasculature, such as endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), as well as inflammatory cells including lymphocytes and monocytes and macrophages (MPs) encounter multiple pathogenic inputs in the patient with diabetes, including elevated free fatty acids (FFAs), dyslipidemia, hyperinsulinemia, hypertension (HTN), increased cytokines, and altered adipokine levels. As such, resolving whether diabetic atherosclerosis represents unique pathogenic mechanisms or similar proatherosclerotic responses amplified by these stimuli remains unclear. Central issues related to diabetic atherosclerosis focused on in this chapter are schematized here. The dyslipidemia of diabetes is characterized by elevated triglycerides, decreased high-density lipoprotein (HDL), and low-density lipoproteins (LDLs) that may be smaller, denser, and more pathogenic. Diabetes involves a fundamental shift to a more prothrombotic state, as evident in platelet biology. The endothelium is an integral player in vascular health; endothelial dysfunction often characterizes diabetes and involves both abnormal vasomotor function and also metabolic abnormalities. Inflammatory responses (highlighted in red) appear particularly involved in diabetic atherosclerosis, with inflammatory changes evident in the endothelium and in lymphocytes (T cells, B cells), monocytes, and monocyte-derived macrophages. In addition to these complexities, it is also important to note that atherosclerosis in diabetes is also influenced by "far-field" effects from other organs, including adipocytes and adipose tissue (e.g., adipokines, FFA release), hepatocytes (coagulation factor production, very low-density lipoprotein [VLDL] secretion), skeletal muscle (insulin resistance), pancreatic islets (insulin release), and bone marrow (progenitor cells). BP = Blood pressure.

be postprandial excursions in TG levels, which may be more predictive of CV risk than the fasting levels usually obtained in the clinic.[7–9]

Lipoprotein lipase (LPL), a key enzyme involved in hydrolyzing fatty acids from TGs and delivering these fatty acids to tissues, may be defective in T2DM. It is interesting to note that LPL-mediated hydrolysis of TGs has been shown to be a mechanism for generating natural ligands for the nuclear receptor known as peroxisome proliferator-activated receptor alpha (PPAR-α), which, when activated by ligands, controls the expression of multiple genes involved in lipid metabolism, inflammation, and fatty acid oxidation.[10–13] Fibrates, lipid-lowering agents used to treat hypertriglyceridemia, are thought to work as PPAR-α agonists.[14,15] Of note, other endogenous lipolytic pathways including adipose tissue TG lipase (ATGL) and hepatic lipase as well as fatty acid synthase can generate PPAR ligands in different physiologic contexts as well.[16–18] These lines of evidence suggest that in diabetes, loss of endogenous LPL action decreases activation of the PPAR-α–regulated gene cassette, which would be predicted to result in decreased expression of apolipoprotein (apo) A-I, which is involved in HDL function, and increased endothelial inflammation. It is important to note that fibrates, as synthetic PPAR-α agonists, may not faithfully replicate cellular responses to natural PPAR-α ligands. Of interest, the potential role of LPL has expanded to include other proteins involved in LPL action. For example, C-III is an endogenous inhibitor of LPL activity. Recent studies implicate apo C-III in promoting proatherogenic, proinflammatory responses, which may occur through various mechanisms, including potential modulation of endogenous PPAR responses as outlined previously as well as other means.[19]

Given that HDL cholesterol levels are inversely associated with coronary heart disease (CHD) risk, significant effort has focused on the mechanisms underlying the low HDL commonly observed in patients with diabetes.[20] Both abnormal production of HDL and remodeling of this lipid by plasma enzymes may contribute to the low level of circulating HDL cholesterol observed in T2DM. Expression and activity of endothelial lipase (EL), a phospholipase that is synthesized in and expressed on the surface of vascular endothelium, catabolizes HDL, resulting in decreased levels of this putatively antiatherogenic lipoprotein. Elevated concentrations of EL protein are significantly correlated with coronary artery calcification score as well as other features of metabolic syndrome including waist circumference, blood pressure, TGs, HDL levels, and fasting glucose in individuals with a family history of premature CHD.[21] In addition, direct correlations have been observed between EL levels and circulating markers of inflammation including high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and soluble intercellular adhesion molecule. Low-dose endotoxemia in 20 subjects increased EL concentrations 12 to 16 hours after injection, and this increase in EL correlated with reductions in plasma HDL.[22–24] Collectively these data suggest that low-intensity inflammation, a common feature of T2DM, controls HDL through effects on EL, providing a possible mechanism for the low HDL in T2DM and the exaggerated CV risk associated with insulin-resistant

states including metabolic syndrome and diabetes mellitus. Despite the clear epidemiologic inverse association between HDL and CV risk, the hypothesis that raising HDL can reduce CV events has not yet been proven. The recent failure of large randomized, placebo-controlled trials designed to test this hypothesis using cholesteryl ester transfer protein (CETP) inhibitors and niacin, which both raise HDL cholesterol levels, suggests that the biology of HDL's atheroprotective effects are likely very complex and cannot be ascribed exclusively to a single parameter such as HDL cholesterol quantity—the current lipid parameter measured in the clinic.[25,26]

Another input into diabetic dyslipidemia is hepatic dysregulation, itself a consequence of fatty liver, hyperinsulinemia, and hyperglycemia.[27] Hyperglycemia per se can alter the carefully controlled system of lipid metabolism, as, for example, through the glycation of proteins and lipoproteins. In addition to altering the normal function of these entities, the breakdown of glycated proteins and lipoproteins, known as advanced glycation endproducts (AGEs), activates specific receptors for AGEs (RAGEs), resulting in responses closely linked to atherosclerotic complications, such as increases in matrix metalloproteinases (MMPs) thought to promote plaque destabilization and rupture.[28–30]

Although total LDL-C levels are often average in patients with T2DM, LDL continues to appear as a significant predictor of CV risk in this patient population. As is usually seen with higher TG values, LDL particles in T2DM are considered more pathogenic as a result of their being smaller, more dense, and hence more prone to entry, oxidation, and retention in the arterial wall.[31] The notion that lipoprotein retention in the subendothelial space may contribute to atherosclerosis may be especially relevant in diabetes. Extensive evidence implicates the oxidation of LDL as a major player in atherosclerosis. Given that hyperglycemia and other aspects of diabetes may promote altered redox balance and increased oxidative stress, increased LDL oxidation in diabetes may be an additional factor in diabetic atherosclerosis. An intriguing newer direction for this field has been evidence that autoantibodies to oxidized LDL (oxLDL) may be involved in atherosclerosis and coronary calcification, which may extend to diabetes, including T1DM.[32]

Placing lipid metabolism into a broader context, lipoprotein particles can be reconsidered as circulating, biologically active entities whose very nature and function afford systemic pathologic effects. Lipoproteins in various forms exit the liver and interact with the vasculature. In their transit through the circulation, lipoproteins also encounter other factors in addition their interactions with vessel walls, including circulating cells and many other proteins. In this regard, one functional unit with which lipoproteins interact is the coagulation system, including both the relevant procoagulant and anticoagulant proteins as well as platelets. Consistent with this concept, studies have reported increased platelet reactivity and thrombogenicity in response to VLDL and TG-rich lipoproteins. Such interactions connect dysregulated lipid metabolism in diabetes to a potent force in atherosclerosis strongly suggested as being altered in the diabetic milieu, namely the coagulation system.

This brief preceding overview underscores the extent to which pathogenesis in diabetes, including alterations in lipid and cholesterol metabolism, are influenced by diverse, often overlapping issues.

DIABETES: A PROTHROMBOTIC STATE

T2DM is characterized by a prothrombotic and hypercoagulable state that is a significant contributor to the pathogenesis and progression of diabetic vascular complications. Multiple factors have been implicated in promoting the prothrombotic state in diabetes, including platelet hyperreactivity, increased coagulation, and impaired fibrinolysis. Although hyperglycemia itself may be a major factor in these pathways, as noted, other components of the clinical picture in diabetes, such as lipid abnormalities, obesity, and inflammation, as well as more specific pathogenic mechanisms such as oxidative stress may also contribute to the prothrombotic, procoagulant state found in those with diabetes, including changes in platelet function, changes in coagulation factors, and shifts in the fibrinolytic balance, as are considered here.

Altered Platelet Function

Platelets of patients with T2DM are characterized by dysregulation of several signaling pathways, leading to hyperreactive platelets with enhanced adhesion, aggregation, and activation (**Fig. 10-2**). Processes that define the diabetic state—hyperglycemia, insulin resistance, dyslipidemia, inflammation, and increased oxidation— are all implicated in platelet hyperactivity in diabetes. Hyperglycemia increases platelet reactivity by altering different biochemical pathways, including protein kinase C (PKC) activation, with subsequent increased platelet granule release and aggregation.[33,34] Glucose also has direct osmotic effects that can increase platelet reactivity.[35] In addition, by inducing nonenzymatic glycation of proteins on the surface of platelets, hyperglycemic states may decrease membrane fluidity while increasing adhesion and activation.[36] Consistent with these findings, acute hyperglycemia has been shown to increase markers of platelet activation such as P-selectin and CD40 ligand, whereas improved glycemic control may decrease platelet reactivity.[37,38]

Platelet aggregation is mediated by platelet surface receptors and adhesive proteins such as glycoproteins GPIIb/IIIa, GPIb, and P2Y12, each of which is altered in T2DM. Platelet turnover in patients with diabetes appears accelerated. Hyperglycemia increases the release of reticulated, larger, and thus more reactive platelets, including a higher capability of forming thromboxane—a potent vasoconstrictor and proaggregant. Diabetic platelets may also have altered signaling through the P2Y12 pathway, a key player in adhesion, aggregation, and procoagulant activity.[39] Increased levels of circulating microparticles, derived from platelets and various stimulated cell types, may also underlie the procoagulant potential in diabetes.[40] Microparticle size is larger in those with T2DM than in normal controls, and increases in microparticle number have been associated with an increased incidence of diabetic complications.[41]

Intracellular calcium is a central mechanism for regulating platelet function. Platelets in patients with diabetes contain lower cyclic adenosine monophosphate (cAMP) levels and higher intracellular calcium levels than in normal patients, which may contribute to hyperreactivity, increased aggregation and activation, and stimulation of thromboxane synthesis.[42] Altered calcium homeostasis may be in part attributable to changes in the activity of calcium ATPases, which are highly sensitive to oxidative damage.[43,44] Recent

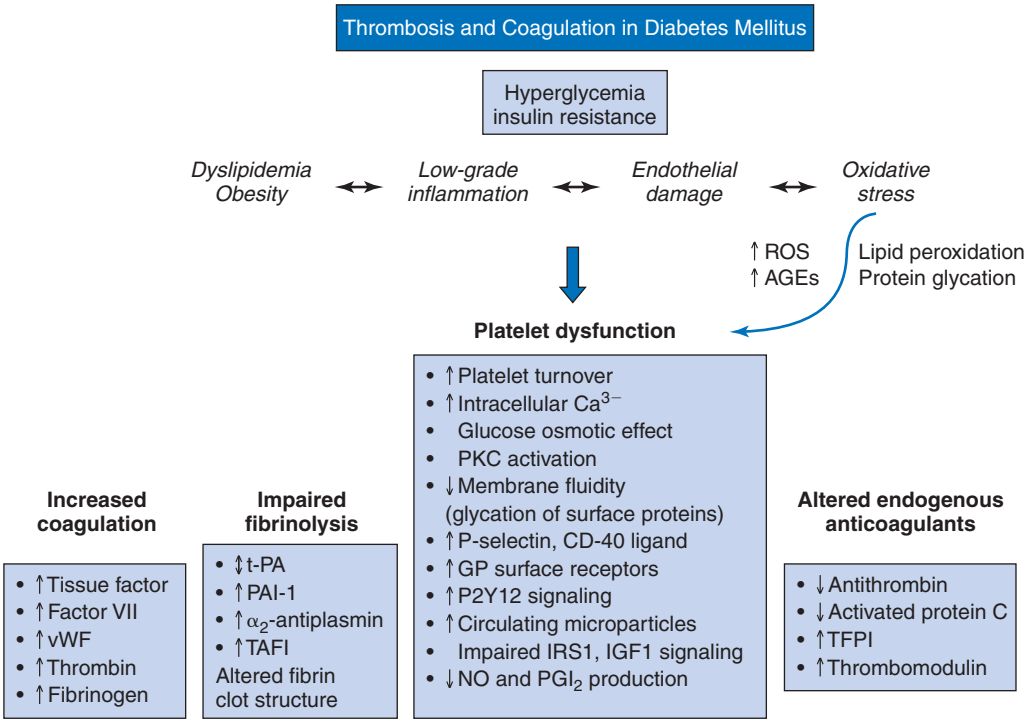


FIGURE 10-2 Abnormal thrombosis and coagulation in diabetes. Many pathologic inputs in diabetes contribute to platelet dysfunction and hypercoagulability, all of which drive a prothrombotic phenotype in patients with diabetes. Hyperglycemia and insulin resistance, a fundamental pathophysiologic feature of diabetes, drives inflammation, dyslipidemia, endothelial dysfunction, and oxidative stress. Each of these stimuli activates platelets by increasing expression of surface receptors for aggregation, increasing production of vasoactive molecules, reducing nitric oxide bioavailability. Simultaneously, production of coagulation factors by ECs including von Willebrand factor (vWF) and tissue factor, along with fibrinogen and factor VII from other sources, enhances coagulation. Lastly, a defect in endogenous fibrinolysis through increased PAI-1 expression tPA all conspire to heighten thrombosis in diabetes. AGEs = Advanced glycation end products; GP = glycoprotein; IGF-1, insulin-like growth factor 1; IRS-1 = insulin substrate receptor 1; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor 1; PGI_2 = prostaglandin I_2; PKC = protein kinase C; ROSs = reactive oxygen species; TAFI = thrombin-activatable fibrinolysis inhibitor; TFPI = tissue factor pathway inhibitor; t-PA = tissue plasminogen activator.

research suggests that activity of calcium-activated proteases (calpains) is increased in platelets from diabetic patients, contributing to dysregulation of platelet calcium signaling and hyperreactivity of platelets.[45]

Insulin resistance and insulin deficiency can both alter platelet reactivity. Insulin opposes the effects of platelet agonists through activation of an inhibitory G protein by insulin receptor substrate 1 (IRS-1). During insulin resistance, impaired insulin receptor signaling attenuates insulin-mediated antagonism of platelet activation, thus increasing platelet reactivity. Insulin-like growth factor 1 (IGF-1), which is present in granules of platelets with IGF-1 receptors present on the platelet surface, stimulates tyrosine phosphorylation of IRS, potentiating platelet activation.[46,47] Reduced insulin sensitivity in platelets lowers cAMP levels and increases intracellular calcium levels, enhancing platelets degranulation and aggregation. In addition, platelets from insulin-resistant patients display diminished sensitivity to the actions of nitric oxide (NO) and prostacyclin while also manifesting significantly lower platelet NO-synthase activity.[48]

As noted, some of the systemic abnormalities often concomitant with diabetes can also alter platelet biology. Hypertriglyceridemia increases platelet reactivity, perhaps in part through apo E.[49] Glycation of LDL particles may also lead to impaired NO production and increased intraplatelet calcium concentration, with subsequent increased platelet hyperreactivity and microparticle formation in diabetic patients.[50] Central obesity appears to promote platelet dysfunction, with reduced platelet sensitivity to insulin, impaired platelet responses to nitrates and prostacyclin, elevated platelet count and volume, increased cytosolic calcium concentration, and evidence for increased oxidative stress.[51] Furthermore, weight loss reverses some of these changes, reducing platelet activation.[52] Increased platelet reactivity has been tied to increased oxidative stress found in T2DM.[53,54] Superoxide and reactive oxygen species (ROSs) may increase platelet reactivity by enhancing postactivation intraplatelet activation calcium.[44] In addition, lipid peroxidation and protein glycation may affect platelet activation.[55] Inflammation may foster platelet reactivity by increasing expression of mediators of platelet activation, such as CD40 ligand, whose plasma-soluble levels are increased in T2DM. CD40L, found in activated platelets, has proinflammatory properties.[56]

Increased Coagulation Factors

The coagulation system involves a complex cascade of procoagulant proteins that ultimately result in thrombin generation and conversion of fibrinogen to fibrin, and formation of fibrin clots. Increased activation of prothrombotic coagulation factors has been reported in T2DM (see **Fig. 10-2**). For example, tissue factor, expressed by endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), is a potent procoagulant that can initiate the thrombotic process. In healthy individuals, tissue factor synthesis was reported to be inhibited by insulin, with platelets from T2DM patients found to produce more tissue factor than platelets from matched controls.[57] The increased level of circulating tissue factor observed in T2DM has been associated with hyperglycemia and hyperinsulinemia in an additive



manner.[58] AGEs, discussed earlier, can contribute to the activation of surface clotting factors.[28] AGEs and ROS can promote tissue factor expression by activating nuclear factor kappa B (NF-κB) transcription factors.

In addition to tissue factor, many other coagulant proteins are implicated in the prothrombotic state of T2DM. Factor VII, which has been associated with increased fatal cardiac events, is elevated in hyperglycemia, insulin resistance, and T2DM.[59,60] Factor VII activity levels in patients with diabetes was shown to be independently associated with hypertriglyceridemia.[61] Factor XIII, activated by thrombin, produces multiple cross-links in the fibrin clot, increasing resistance to lysis. Factor XIII subunit levels were shown to correlate with features of the metabolic syndrome and insulin resistance. In addition, there is some evidence for association between factor XIII polymorphisms and the risk of thrombotic vascular diseases.

Von Willebrand Factor and Fibrinogen

Von Willebrand factor (vWF), which promotes platelet adhesion by binding to the platelet glycoprotein GPIb receptor and is associated with EC damage, has been linked to atherosclerosis and future CV events.[62] vWF levels may be increased in insulin resistance and T2DM. Increased platelet thrombin, which converts fibrinogen to fibrin, has been found in association with hyperglycemia. Thrombin is increased in patients with diabetes, including as a function of glucose control.[37,63] Thus, improved glycemic control may reduce blood thrombogenicity.[64] Fibrinogen, an acute-phase protein that independently predicts future CV events, is elevated in diabetic patients and is associated with microvascular and macrovascular complications.[65–68] Glycemia and insulin resistance correlate with increased fibrinogen levels.[69] Mechanisms that may explain the increased fibrinogen levels observed in T2DM include enhanced fibrinogen production facilitated by hyperinsulinemia and the low-grade inflammation often found in T2DM.[70] IL-6 cytokine levels, which are elevated in T2DM, can stimulate hepatocytes to produce fibrinogen, connecting between inflammation and hypercoagulation. Despite these findings, evidence that improved glycemic control reduces fibrinogen levels remains to be established.[71]

Changes in Endogenous Anticoagulants

The prothrombotic state of T2DM involves not only increases in procoagulants, but also changes in endogenous anticoagulants, such as antithrombin, tissue factor pathway inhibitor (TFPI), protein C, and thrombomodulin, which help maintain the physiologic balance in coagulation. Antithrombin inhibits thrombin by forming a stable complex with thrombin and other coagulation factors, and inhibits factor VII bound to tissue factor. Diabetic patients reportedly have reduced antithrombin anticoagulant activity.[72] Hyperglycemia may also induce conformational changes to antithrombin, leading to its retention and aggregation.[73] Suggested mechanisms of the glucose effects on antithrombin are nonenzymatic glycation and endoplasmic reticulum (ER) stress induced by hyperglycemia.

The endogenous anticoagulant TFPI, produced mainly in ECs and associated with atherosclerosis, inhibits tissue factor–initiated coagulation by binding with activated factor X and modifying the activity of factor VII–tissue factor catalytic complex.[74,75] TFPI circulates primarily bound to lipoproteins in the plasma. Increased levels of atherogenic lipoproteins have been associated with a shift of the tissue factor–TFPI balance toward higher plaque thrombogenicity.[76] Increase in TFPI activity was also demonstrated in patients with T1DM, a hypothesized consequence of increased thrombin formation and altered binding of TFPI to glycosaminoglycans after vascular damage.[77] Other recently identified noncoagulant roles of TFPI, including action in inflammation, angiogenesis, and lipid metabolism, may be associated with vascular damage in diabetes.[78]

Activated protein C (APC), converted from protein C by the action of the thrombin-thrombomodulin complex present on ECs, functions as an anticoagulant by inactivating the coagulation factors V and VIII. APC may also have profibrinolytic activity by inactivating plasminogen activator inhibitor type 1 (PAI-1) in addition to having anti-inflammatory, antioxidant and cytoprotective properties.[79,80] A recent study suggested that low protein C levels are a risk factor for incident ischemic stroke but not CHD.[81] Decreased APC generation has been reported to be associated with progressive atherosclerosis in T2DM.[82]

As noted, thrombomodulin, a membrane protein synthesized predominantly by ECs, is a cofactor for thrombin-mediated activation of protein C, and also reduces procoagulant activities such as fibrinogen clotting, factor V, and platelet activation. Thrombomodulin also exerts important effects that modulate cellular proliferation, adhesion, and inflammation and may serve as a marker for endothelial damage.[83] However, the association between circulating levels of thrombomodulin and incident CHD is controversial.[84,85] In healthy individuals, researchers have demonstrated an inverse association between soluble thrombomodulin levels and risk for future T2DM.[86] However, in patients with T2DM, plasma thrombomodulin levels were increased and positively correlated with the metabolic syndrome.[87] Elevated plasma concentrations of soluble thrombomodulin in T2DM may reflect enhanced hypercoagulability and altered fibrinolysis.[88]

Impaired Fibrinolysis

The maintenance of blood flow involves a coordinated balance between clot formation and clot removal. Fibrinolysis, the process of clot dissolution and removal, involves a cascade of interacting proenzymes and enzymes. Inhibition of fibrinolytic pathways promotes clot formation; shifts in fibrinolytic balance have been strongly implicated in atherothrombosis. Impairment of fibrinolysis has been noted in T2DM, and hypofibrinolysis is a risk factor for the development of CV complications in patients with diabetes.

Changes in glucose concentrations can induce modifications in the fibrin network that promote thrombosis.[89] Fibrin clots in patients with diabetes are altered in structure, with a more compact structure, decreased pore size of the clot matrix itself, and resistance to fibrinolysis, resulting in longer time to clot lysis as compared with healthy controls.[90] Furthermore, improving glycemic control in T2DM has been suggested to result in a more benign clot structure.[91]

The balance between clot formation and dissolution involves important offsetting action between tissue plasminogen activator (t-PA) and PAI-1. t-PA, produced by ECs, mediates the conversion of plasminogen to plasmin and is the main factor responsible for initiating the fibrinolytic process. PAI-1 regulates fibrinolysis by binding to t-PA, blocking

the conversion of plasminogen into active plasmin, and thus inhibiting fibrinolysis. It is interesting to note that PAI-1 is also produced by adipocytes, making it of obvious significance as a potential link between diabetic adiposity and CVD. In general, both t-PA and PAI-1 are linked to increased risk of CV events as well as a worse postevent prognosis,[92,93] although this issue is not without controversy.[94] PAI-1 is elevated in insulin-resistant states, correlates strongly with components of the metabolic syndrome, and may predict future T2DM.[95,96] Hyperglycemia and hyperinsulinemia, by increasing expression and activation of proinflammatory forces such as the transcription factor NF-κB as well as PAI-1, reduce the activity of t-PA and shift fibrinolytic balance toward thrombosis. Glucose-lowering effects have been reported to reduce PAI-1 levels.[97]

Although t-PA, and its relationship with PAI-1 are critically important to the thrombotic state, other endogenous anticoagulants have also been suggested as contributing to increased atherothrombosis in diabetes. For example, thrombin-activatable fibrinolysis inhibitor (TAFI) is a proenzyme activated by the thrombin-thrombomodulin complex. TAFI inhibits fibrinolysis by cleaving lysine residues on fibrin, thus preventing t-PA and plasminogen binding. Increased plasma TAFI levels were reported in insulin resistance and T2DM patients.[98,99] However, studies report inconsistent results regarding the role of TAFI levels and activation in thrombosis, especially in coronary artery disease.[100] Alpha$_2$-antiplasmin is the main physiologic inhibitor of plasmin. Elevated alpha$_2$-antiplasmin levels may correlate with the risk of myocardial infarction (MI).[101] Moreover, generation of plasmin–alpha$_2$-antiplasmin complex, which reflects reactive fibrinolysis, was shown to be associated with subclinical atherosclerosis and incidence of coronary disease in small studies.[102–104] Nevertheless, the role of alpha$_2$-antiplasmin in the risk of arterial thrombosis remains unresolved. Limited studies suggest the possibility of changes in alpha$_2$-antiplasmin in T2DM. In general, global assessment of whole plasma fibrinolytic potential may provide stronger evidence linking fibrinolysis to arterial thrombosis than separate evaluation of individual fibrinolytic factors, with further such studies needed in T2DM[105] (**Table 10-1**).

ENDOTHELIAL FUNCTION AND DYSFUNCTION IN DIABETES

It is worthwhile noting that the processes of coagulation and lipid metabolism discussed here, with their elaborate, carefully controlled steps that are altered in T2DM, are carried out to a significant extent on the endothelial surface. A central tenet of our evolved view of the vasculature and atherosclerosis is that the endothelium is not a simple platform but rather a dynamic, reactive organ engaged in endocrine, paracrine, and autocrine function. Given its anatomic position in the vasculature, the single-cell-thick endothelium, which lines the entire vascular tree, can be understood as a transducer of components of the circulation, including circulating mediators of risk such as glucose, FFAs, and pathogenic lipoproteins. As the physical barrier separating flowing blood from the vessel wall, the endothelium is uniquely positioned to control homeostatic processes including blood pressure, hemostasis, and homing of immune cells to sites of inflammation. When dysregulated, all of these processes can contribute to the development of atherosclerosis and have been especially implicated in diabetic atherosclerosis (**Table 10-2**). In this context, it is especially significant to note studies that suggest abnormal endothelial responses among the earliest precursor abnormalities found in seemingly healthy individuals ultimately destined to develop diabetes. For example, in one clinical study, flow-mediated endothelium-dependent vasodilation (EDV) was 38% lower in patients with a family history of T2DM in both parents (+FH) versus those with no family history of diabetes.[106] Of importance, the +FH group did not carry a diagnosis of diabetes, although fasting blood sugar was somewhat higher (5.3 versus 4.9 mmol/L).

The control of vascular resistance by the endothelium is essential for maintaining mean arterial pressure and for autoregulating flow regionally to different tissues depending on metabolic demands. ECs synthesize NO from L-arginine by the action of the Ca^{2+}-dependent, endothelial-specific nitric oxide synthase isoform (eNOS) in response to changes in blood flow.[107] Once formed, NO activates soluble guanylate cyclase located in adjacent VSMCs, leading to increased cyclic guanosine monophosphate (cGMP) levels, smooth muscle cell (SMC) relaxation, and functional vasodilation. This process is dependent on intact vascular endothelium and is a defining feature of normal endothelial function (**Fig. 10-3**).[108,109] As discussed later, endothelial dysfunction, among the earliest features of atherosclerosis and especially diabetic atherosclerosis, manifests as loss of flow-mediated vasodilation, which can be measured noninvasively by brachial artery ultrasound. ECs produce other important vasoactive mediators, including prostacyclin and endothelium-derived hyperpolarizing factor (EDHF), that couple tissue blood flow to metabolic demands. In response to stimuli including proinflammatory cytokines, the vascular endothelium also elaborates vasoconstrictors including endothelin-1, angiotensin II, thromboxane A_2, and isoprostanes that increase vascular tone, permeability, hemostasis, and inflammation. The balance of these vasodilator and vasoconstrictor factors is pivotal for maintaining arteriolar resistance and establishing mean arterial blood

TABLE 10-1 Impaired Fibrinolysis in Diabetes

FIBRINOLYTIC FACTORS	FUNCTION	IMPAIRMENT IN DIABETES	POSSIBLE UNDERLYING MECHANISMS FOR IMPAIRED FIBRINOLYSIS
t-PA	Clot lysis (converts plasminogen to plasmin)	↕	Endothelial cell dysfunction (t-PA)
PAI-1	Inhibition of clot lysis (binding to t-PA, blocking the conversion of plasminogen into plasmin)	↑	Inflammatory response Protein glycation (plasminogen)
TAFI	Cleaves lysine residues on fibrin, preventing t-PA and plasminogen binding	↑	Hyperglycemia and insulin resistance
Alpha$_2$-antiplasmin	Physiologic inhibitor of plasmin	↑	Increased secretion by adipocytes (PAI-1) Altered clot structure, ↓ pore size, ↑ clot-lysis time

TABLE 10-2 Resident Vascular Cells, Cells of Innate and Adaptive Immunity, and the Pathways and Mediators Dysregulated in the Diabetic State

VASCULAR CELL	PATHWAYS	MEDIATORS	REFERENCES
Endothelium	Leukocyte trafficking Vascular reactivity Inflammation Metabolism Redox signaling Biomechanical forces Apoptosis Thrombosis and fibrinolysis	E-selectin P-selectin VCAM-1 ICAM-1 NF-κB eNOS, nitric oxide EDHF FoxO PPAR-γ, PPAR-α SOD PAI-1, t-PA Thrombomodulin vWF Tissue factor	107, 111, 119, 124, 125, 136, 144, 190
VSMCs	Inflammation Vascular reactivity Matrix remodeling Proliferation and migration	iNOS, nitric oxide MCP-1 IL-6 TGF-β Collagen MMPs PDGF	169–171, 191, 192
Monocyte/Mϕ	Inflammation NLRP3 inflammasome Matrix remodeling Autophagy ER stress, UPR Lipid transport	IL-6 TNF-α IL-1β MMP COX-2 Toll-like receptors CHOP/caspase/JNK PPAR-α, PPAR-γ, PPAR-δ FABPs	156, 161, 164, 189, 193, 194
Lymphocyte	Inflammation T and B cell proliferation Autoimmunity	IFN-γ IL-17 LDL autoantibodies	32, 130
Platelet	Thrombosis Microparticles	Nitric oxide Thromboxane A_2 IGF-1 Calpains P-selectin Protein kinase C P2Y12	39, 47, 49, 56, 57, 68, 85, 195

Endothelial dysfunction, a seminal event in diabetic atherogenesis, involves loss of nitric oxide and proinflammatory gene expression including adhesion molecule expression that promotes leukocyte homing to nascent plaque. Activation of master transcription factors including NF-κB, PPAR-γ, and Forkheads (FoxO) by glucose, lipoproteins, FFAs, and insulin drive this phenotypic change that encompasses endothelial dysfunction. Vascular smooth muscle cells proliferate and secrete matrix proteins in response to the same stimuli in diabetes, enlarging the neointima. Monocyte recruitment through chemokines such as MCP-1 leads to macrophage foam cell formation in the growing plaque. Emerging literature has demonstrated an important role for autophagy and ER stress responses in regulating macrophage inflammation, apoptosis, and plaque stability in atherosclerosis. Finally, lymphocytes are primed to produce autoantibodies and secrete proinflammatory cytokines including IFN-γ that worsen plaque inflammation. Patients with diabetes also have higher thrombosis risk. Platelet dysfunction occurs through activation of multiple pathways including calpains, PKC, IGF-1 and enhanced production of vasoconstrictor lipids such as thromboxane. CHOP = C/EBP homologous protein; COX-2 = cyclooxygenase 2; EDHF = endothelium-derived hyperpolarizing factor; eNOS = endothelial isoform of nitric oxide synthase; ER = endoplastic reticulum; FABPs = fatty acid binding proteins; ICAM-1 = intercellular adhesion molecule-1; IFN-γ = interferon gamma; iNOS = inducible macrophage-type nitric oxide synthase; JNF = c-Jun N-terminal kinase; MCP-1 = monocyte chemoattractant protein 1; NLRP3 = Nod-like receptor protein 3; PDGF = platelet derived growth factor; SOD = superoxide dismutase; TGF-β, transforming growth factor beta; TNF-α = tumor necrosis factor alpha; UPR = unfolded protein response; VCAM-1 = vascular adhesion molecule-1; VSMCs = vascular smooth muscle cells.

pressure. NO also reduces platelet aggregation and leukocyte adhesion, thereby suppressing endogenous thrombus formation, maintaining blood rheology, and suppressing leukocyte accumulation in the vessel wall. As discussed further later, extensive evidence implicates shifts in all these components of normal endothelial function in the setting of diabetes and its associated abnormalities.

In addition to helping control vascular homeostasis, the endothelium also plays a part in host response to inflammation by regulating leukocyte trafficking to sites of injury. Proinflammatory signals including interleukin 1-beta (IL-1β), tumor necrosis factor α (TNF-α), and oxLDL induce EC expression of genes involved in leukocyte homing and diapedesis, a multistep and orchestrated process collectively known as the *leukocyte adhesion cascade*. The induction of specific endothelial gene networks, composed of key mediators of leukocyte adhesion such as E-selectin, P-selectin, vascular adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), along with chemoattractants such as IL-8 and monocyte chemoattractant protein 1 (MCP-1), coordinate each aspect of leukocyte rolling, firm adhesion to ECs, and transmigration into the vessel wall.[110] The ability of neutrophils, monocytes, and lymphocytes to home to local areas of inflammation is vital to host defense during acute inflammatory responses. However, this endothelial activation becomes maladaptive in chronic states of inflammation, such as encountered in atherosclerosis and in particular perhaps diabetic atherosclerosis, enabling monocytes or other immune cells to accumulate within the vessel wall and propagate

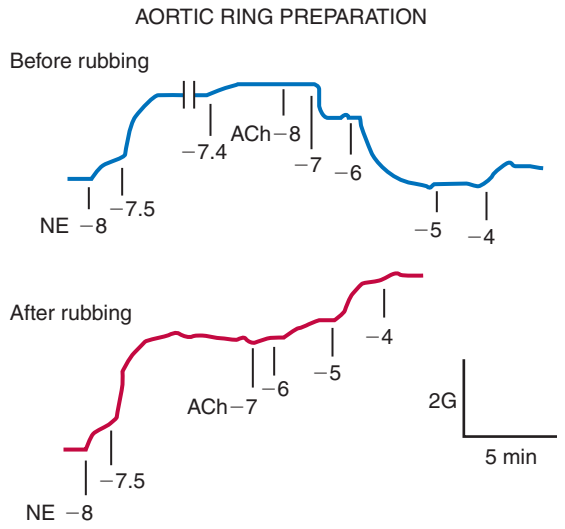


FIGURE 10-3 Endothelial-dependent vasodilation and the importance of endothelial function. Pioneering work by Furchgott and colleagues identified the critical importance of endothelial cells, the single-cell-thick layer lining the vascular tree, in maintenance of vasomotor tone. Serendipitously, these investigators discovered that acetylcholine treatment of isolated aortic rings isolated from rabbit induced vasodilation or vasoconstriction depending on whether the intimal cell layer was intact or accidentally rubbed off during the tissue preparation. This observation identified a novel role for endothelium, at the time considered only a passive cell layer, and also ushered in a new era in vascular biology and led to the eventual discovery of nitric oxide—a key regulator of vascular homeostasis. Now, the vascular endothelium is understood to be a dynamic organ that regulates (1) vascular tone, (2) inflammatory responses through recruitment of leukocytes to sites of injury including in atherosclerosis, (3) nutrient availability for metabolically active tissues such as fat and muscle, (4) resident vascular cell proliferation, and (5) thrombosis and platelet aggregation. Endothelial dysfunction is one of the earliest features of diabetic (and nondiabetic) atherosclerosis and can be measured noninvasively with brachial artery ultrasound, or invasively with acetylcholine (Ach) infusion during coronary artery angiography. Normal endothelial function results in vasodilation after Ach, whereas endothelial dysfunction results in paradoxical vasoconstriction. More recent work suggests that endothelial function may more broadly encompass regulation of systemic metabolic responses including fatty acid transport and adiposity. NE = Norepinephrine. *(From Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine,* Nature *288:373-376, 1980.)*

atherosclerotic plaque as well as plaque rupture. Most of the abnormalities associated with T2DM—hyperglycemia, elevated FFAs, hypertriglyceridemia, hypertension—have all been linked to an activated endothelial state.

A major factor promoting insight into the role of the endothelium in atherosclerosis as well as diabetic atherosclerosis has been the ability to measure endothelial function, either invasively in the cardiac catheterization laboratory or noninvasively with techniques such as brachial artery ultrasound. These techniques build on the seminal observations that after removal of just the endothelium in arterial preparations, the normal vasodilatory response to substances such as acetylcholine became paradoxical, resulting in vasoconstriction.[108] Quantitative coronary angiography can document the change in vascular diameter in response to acetylcholine (or bradykinin, substance P, or serotonin). In patients with endothelial dysfunction, the vasodilator response to acetylcholine is blunted, or results in paradoxical vasoconstriction. In brachial artery ultrasound, forearm blood flow is occluded for 5 minutes with use of a sphygmomanometer, maintained at constant pressure. After release of the cuff, reactive hyperemia ensues, leading to endothelium-dependent, flow-mediated NO production and vasodilation, measured by an increase in artery diameter on ultrasound. In patients with endothelial dysfunction, these responses are severely blunted.

Endothelial dysfunction is a defining feature of early atherosclerosis in diabetic patients and also occurs in the presence of other traditional CV risk factors such as hypertension and hyperlipidemia.[111,112] Mechanistically, endothelial dysfunction results from a loss of NO bioavailability, which can occur through impaired production by eNOS or increased degradation. As a consequence, the atheroprotective effects of NO including vasodilation, inhibition of thrombosis or aggregation, and suppression of leukocyte adhesion to the vessel wall are lost. There are multiple metabolic derangements common to T2DM and metabolic syndrome including insulin resistance, hyperglycemia, high circulating FFA levels, and elevated levels of ROSs that all contribute to loss of NO and endothelial dysfunction in patients with diabetes.[113,114] The specific role of hyperglycemia and insulin resistance in vascular function is discussed elsewhere. The infusion of FFAs reduces EDV in animal models and in humans.[115] FFAs activate PKC, driving signal transduction pathways that reduce NO production by eNOS.[116] The accumulation of lipids in tissues and cells including FFAs, fatty acyl-coenzyme As, and others such as diacylglycerols is termed *lipotoxicity* because of the effect these lipid mediators have on intracellular signal transduction pathways including insulin. Another major cause of reduced NO bioavailability is the formation of peroxynitrite ($ONOO^-$) through the reaction of NO with superoxide anion. High intracellular FFAs result in uncoupling of fatty acid oxidation, which increases levels of free radicals such as superoxide anion (O_2^-). Normally, superoxide is rapidly removed by scavenging enzymes such as superoxide dismutase. When superoxide anion levels rise, as occurs in patients with diabetes in response to elevated FFAs and hyperglycemia, peroxynitrite is formed nonenzymatically at high levels. Other enzymes that increase superoxide, including nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidases and xanthine oxidase, can also indirectly promote formation of peroxynitrite in the setting of diabetes. Once generated, peroxynitrite fosters endothelial dysfunction and vascular disease in several postulated ways.[117–119] Peroxynitrite can trigger apoptosis and cell death in ECs and VSMCs, induce endothelial adhesion molecule expression, and disrupt the endothelial glycocalyx. In addition, peroxynitrite-dependent oxidation of tetrahydrobiopterin, a critical cofactor for eNOS function, uncouples eNOS, leading to production of superoxide instead of NO.[120,121] Lastly, ROSs can enhance proinflammatory gene expression leading to endothelial activation (**Fig. 10-4**).

Alterations in NO bioavailability and the increased nitrosative stress in the form of greater peroxynitrite production and protein nitrosylation contribute to macrovascular disease in diabetes.[122] Increased nitrotyrosine levels are detectable in the plasma of diabetic patients.[123] Levels of nitrotyrosine correlate with cell death in ECs. Neutralization of peroxynitrite improves endothelial dysfunction in murine models of diabetes.

Recent preclinical work also provides another perspective on endothelial dysfunction, namely that this dysfunction may extend beyond altered vasomotor function to also include changes in metabolism. Several recent studies have reported pathways that when altered result in changes in glucose and FFA handling. For example, a loss of PPAR-γ in the endothelium changes lipid metabolism, FFA levels, and adiposity with concomitant changes in diabetes.[124] Other work finds that regulation of insulin receptor adaptor

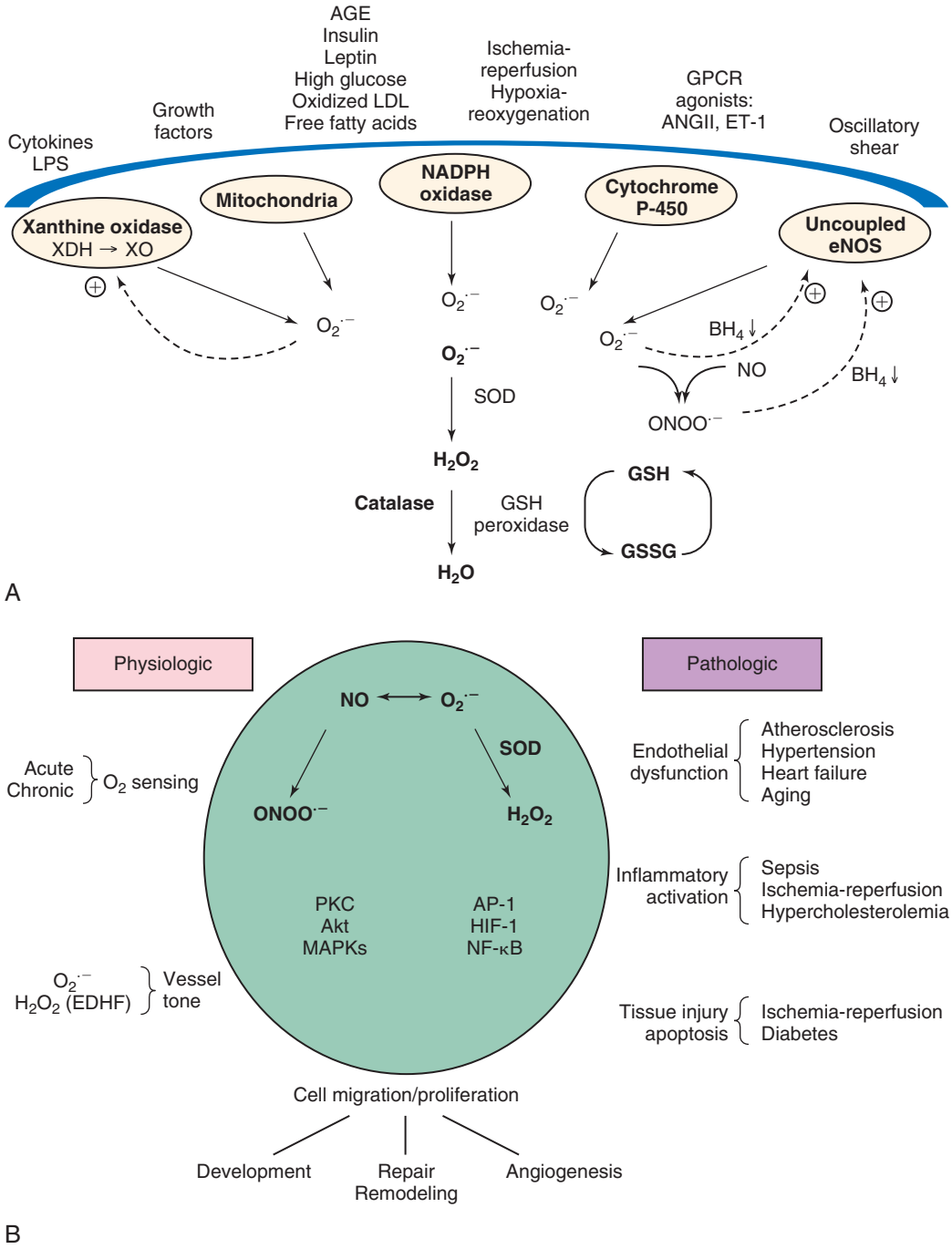


FIGURE 10-4 The role of reactive oxygen species in endothelial dysfunction. A, Multiple inputs including proinflammatory cytokines, growth factors, and metabolites elevated in T2D including free fatty acids and glucose can lead to production of superoxide anion (O_2^-). **B,** Superoxide anion reacts with nitric oxide (NO), reducing NO bioavailability and leading to alterations in vascular tone, endothelial adhesion, angiogenesis, and cell viability. ANGII = Angiotensin II; AP-1 = Activator protein 1; ET-1 = endothelin 1; GPCR = g-protein coupled receptor; GSH peroxidase = monomeric glutathione; GSSG = glutathione disulfide; HIF-1 = hypoxia-induced factor-1; LPS = lipopolysaccharide; MAPKs = mitogen activated protein kinase; XDH = xanthine dehydrogenase; XO = xanthine oxidase. *(From Li and Shah; AJP Regulatory, Integrative and Comparative Physiology 287:R1014-R1030, 2004.)*

proteins in the endothelium (IRS1 and IRS2) by the Forkhead box proteins (FoxO), a family of DNA binding transcription factors that regulate expression of genes involved in growth, proliferation, and metabolism, can mediate atherogenesis. In these studies, deletion of the three genes encoding FoxO isoforms conditionally in the endothelium protects against atherosclerosis while also promoting hepatic insulin resistance.[125,126] These and other studies, by establishing a role for ECs directly in metabolism, force a broader definition of what endothelial dysfunction might represent. Furthermore, these observations link to clinical studies identifying changes in the endothelium as an early and important part of diabetes and not just diabetic atherosclerosis.

Endothelial Adhesion and Inflammation

Endothelial dysfunction is also associated with increased adhesiveness of the endothelium. Indeed, the induction of vascular cell adhesion molecule 1 (VCAM1) messenger RNA (mRNA) and VCAM-1 protein in vascular ECs is one of the earliest molecular events in experimental models of

atherosclerosis such as the Watanabe heritable hyperlipidemic rabbit.[127,128] In humans, adhesion molecule expression can also be detected in atherosclerotic plaque, and circulating levels of soluble adhesion molecules such as VCAM-1 and ICAM-1 positively predict future risk of CVD, as also suggested in T2DM.[129] Aortic endothelium from genetic models of hyperlipidemia such as the LDL receptor null mouse supports greater leukocyte rolling and firm adhesion of leukocytes as determined by mononuclear cell adhesion assays versus aortas from animals with normal lipid levels.[130] Diabetes is associated with activation of the vascular endothelium resulting in enhanced leukocyte adhesion.[131] In diabetes, this activation of the endothelium occurs as a result of many forces including reduced NO bioavailability and the chronic proinflammatory state within the vasculature. Recent work identifies Toll-like receptors (TLRs) as proteins on the surface of ECs and macrophages that bind circulating FFAs and propagate signal transduction cascades that promote proinflammatory gene expression.[132–134] The master transcription factor, NF-κB, mediates multiple proinflammatory responses including those in the endothelium, enhancing expression of adhesion molecules and chemoattractant cytokines, or chemokines, that call monocytes to sites of injury.[135,136] Chemokines such as MCP-1 have been strongly implicated as integral signals in atherosclerosis and diabetic atherosclerosis. Thus, one can understand endothelial activation as enabling a series of steps in response to injury—whether as a result of hyperglycemia, elevated FFAs, hypertension, smoking, or other noxious stimuli—that promote multiple steps of leukocyte trafficking into the vessel wall.[136] In other settings, such responses are integral to host defenses and healing; in the setting of atherosclerosis, such important responses may ultimately prove maladaptive. The influx of leukocytes including monocytes and lymphocytes increases plaque cellularity. Lipid-laden macrophages, termed *foam cells*, phagocytose necrotic cells and free cholesterol in the vessel wall, forming the characteristic atherosclerotic plaque and promoting plaque disruption.[137] Aside from these classic models of atherogenesis, loss of the ECs, known as *superficial erosion*, has been identified as another pathologic mechanism that can also lead to atherosclerotic plaque formation and its complications.[138,139]

Hemodynamic Forces

Early atherosclerotic lesions, known as "fatty streaks," typically form at branch points in the aorta. These regions are characterized by a disturbed blood flow profile that is distinct from the physiologic laminar shear stress in other regions of the aorta. Silver staining of aortic endothelium has revealed that the ECs at these branch points appear irregular in shape, whereas ECs from other regions align in the direction of blood flow. Pioneering research using flow models to study vascular endothelium in vitro has revealed that shear stress forces not only alter EC shape, but also modulate EC gene expression, with the identification of gene regulatory regions modulated in response to distinct patterns of flow.[140] Exposure of static monolayers of cultured ECs to physiologic levels of shear stress results in dynamic induction of genes known to suppress atherogenesis including eNOS, superoxide dismutase, catalase, and TGF-β signaling molecules.[141,142] ECs exposed to disturbed, nonlaminar shear stress fail to express these atheroprotective gene programs. In addition to regulating NO bioavailability by eNOS and the enzymes involved in reducing ROS generation (superoxide dismutase aka SOD, catalase), shear stress also alters NF-κB tissue levels and activation. Confocal microscopy has demonstrated that lesion-prone regions of the aorta, including branch points, are associated with higher levels of nuclear localized, active NF-κB in the endothelium.[143] In addition, the NF-κB–dependent transcriptional responses at these branch points are significantly higher when stimulated by low-level, proinflammatory stimuli, including factors common in patients with diabetes.[143] Enhanced inflammatory signaling through altered NF-κB activation and loss of NO results in heightened endothelial activation and contributes to the endothelial dysfunction observed in early diabetic atherosclerosis. Collectively, these studies reveal that hemodynamic forces have broad effects on endothelial function and inflammation that contribute to the early atherosclerotic plaque formation. Given the frequency of hypertension in T2DM, many of these mechanisms are activated, if not augmented, in patients with diabetes.

INFLAMMATION: A UNIFYING HYPOTHESIS OF DIABETES AND ATHEROSCLEROSIS?

Although early epidemiologic studies identified risk factors associated with CVD (now considered "traditional"), the mechanisms by which hypertension, cigarette smoking, hypercholesterolemia, and T2DM directly promote atherosclerosis remain intensively investigated.[144] By some estimates, 35% of patients may have clinically significant atherosclerosis in the absence of traditional risk factors.[145] Furthermore, despite treatment with maximal medical therapy, patients recovering from an acute coronary syndrome have substantial residual risk of recurrent events.[146] These and other similar observations have stimulated interest in identifying common as well as additional mechanisms driving atherosclerosis in general as well as in the setting of diabetes.

Considerable evidence now points to chronic, low-grade inflammation as a factor in initiating and perpetuating atherothrombosis as well as diabetes itself. For example, in the Physicians' Health Study (N = 22,000 men) and the Women's Health Study (N = 38,000), the relative risk of future MI, stroke, and CV death in these otherwise healthy individuals at baseline was linearly associated with hsCRP across the normal range of hsCRP values (≤3 mg/L).[147,148] Furthermore, this relationship was evident even after other risk factors were controlled for. Similar findings have since been validated in other large cohorts, with only a few controversial exceptions. Other circulating inflammatory biomarkers including IL-6, MMP-9, pentraxin-3, and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and soluble adhesion molecules have demonstrated similar results for predicting CVD risk, albeit with different magnitudes and variable usefulness as clinical tools.[129,149] These results suggest that the clinical observations regarding hsCRP may reflect inflammatory responses in the vasculature. Important to our focus here, hsCRP has also been suggested to be associated with future risk of diabetes. Inflammatory changes have been found in adipose tissue and pancreatic beta cells as well as in other settings that may relate to insulin resistance and beta cell failure.[150]



Notably, infiltration of visceral adipose tissue by macrophages and other leukocytes has been shown to contribute to the systemic proinflammatory state observed in diabetes. Moreover, studies with salicylates, thiazolidinediones, and other agents have raised the question regarding whether treating inflammation can improve the course of diabetes itself.[151] This convergence between diabetes and atherosclerosis around inflammation suggests this as a potentially central component of the common soil long proposed to link diabetes with atherosclerosis and a mechanism worthy of further attention.

Multiple lines of evidence have demonstrated that inflammatory signaling is relevant for the pathobiology of atherosclerosis in T2DM. In a cross-sectional study of 48 patients with T1DM and 66 nondiabetic patients from the Diabetes Control and Complications Trial (DCCT), higher levels of acute-phase proteins including alpha$_1$-acid glycoprotein (53.5 versus 40.0 mg/dL) and hsCRP (0.23 versus 0.14 mg/dL) were found in those with diabetes.[152] No correlation was found between the acute-phase proteins and other demographic, clinical, or laboratory variables including blood cholesterol. The proinflammatory markers such as soluble ICAM-1 and soluble TNF-α receptors (sTNF-α-Rs) are elevated in T2DM. Inflammatory biomarkers measured in DCCT including soluble intercellular adhesion molecule-1 (sICAM-1) sICAM-1 and sVCAM-1 were also found to decrease after intensive glycemic control over a 3-year period.[153] In the case of hsCRP, there was a more complex effect based on change in body weight during the study, suggesting that the effects of glycemic control on inflammation are complex and can be influenced by body weight. Ultimately, from the perspective of vascular biology, the evidence for inflammation as a force contributing to diabetic atherosclerosis can be pursued in terms of specific responses among relevant cellular players including monocytes and macrophages, lymphocytes, VSMCs, and ECs (discussed earlier). The importance of statin therapy in diabetic vascular disease risk reduction is reflected in the most recent ACC/AHA guidelines that identify individuals aged 40–75 with diabetes mellitus and LDL cholesterol between 70–189 mg/dL, but without clinical manifestations of atherosclerotic vascular disease as candidates for treatment with at least moderate if not high intensity (if calculated 10 year risk is greater than or equal to 7.5%) statin. This issue will be addressed in more detail in subsequent chapters.[153a]

Monocyte and Macrophages

Endothelial dysfunction and low-grade inflammation drive the recruitment of monocytes into the vessel wall.[136] Monocyte differentiation into macrophages enables these phagocytes to begin engulfing cholesterol, forming foam cells and the characteristic fatty streak. Formation of foam cells leads to further inflammation within the vessel wall that amplifies initial proatherogenic signals emanating from ECs, circulating monocytes, and lesional macrophages. Notably, the presence of diabetes has been shown to increase peripheral blood monocyte count.[154] Furthermore, in humans with T1DM, circulating levels of monocyte-derived, proinflammatory cytokines are elevated. For example, as compared with controls, TNF-α, IL-6, IL-1β, and IL-1α serum levels have all been shown to be increased.[155] Other proinflammatory biomarkers including hsCRP, sICAM-1, sE-selectin, and sP-selectin are also elevated. Monocytes isolated from human patients with T1DM spontaneously secrete the proinflammatory cytokines IL-1β, IL-6, and TNF-α, which corresponds to increases in gene expression of these molecules.[156] Monocytes isolated from those with diabetes and co-cultured with lymphocytes induced greater levels of IL-17–positive lymphocytes, a population of proinflammatory cells involved in vascular inflammation.[156] Monocytes from patients with diabetes also secrete greater levels of inflammatory cytokines such as IL-6 in response to model stimuli such as lipopolysaccharide (LPS). In this cohort, there was no correlation of levels of CRP, adhesion molecules, and monocyte function with body mass index (BMI) or glycemic control, as measured by hemoglobin A1c or plasma glucose level.

Although monocytes typically constitute only 5% to 10% of circulating leukocytes, they are considered critical determinants of atherosclerosis. Moreover, there exists significant phenotypic heterogeneity within this cell population.[154] In humans, classically activated monocytes (M1 cells) are positive for the surface marker CD14 and negative for CD16 (also known as FcγRIII). M1 cells represent 90% of the entire monocyte pool. Alternatively, activated macrophages (M2 cells) are both CD14 and CD16 positive and serve a posited anti-inflammatory role in tissue patrolling and inflammation resolution. These two monocyte populations also differ in chemokine receptor expression. The CD14+/CD16 − express high levels of C-C motif chemokine receptor 2 (CCR2), the receptor for MCP-1, whereas the CD16+ monocytes express low levels of CCR2, high levels of CCR5, and high levels of the fractalkine receptor CX3CR1. Analogous populations of mouse monocytes have been defined based on the level of the cell surface marker Ly6C. Ly-6Chigh cells correspond to CD14+/CD16 − monocytes, whereas Ly-6Clow cells correspond to human CD14+/CD16+ monocytes. Notably, in murine models of atherosclerosis, such as the apo E–deficient mouse, exposure to a high-cholesterol diet over time results in expansion of the proinflammatory Ly-6Chigh monocyte pool.[157] These monocytes preferentially expand in number and home to atherosclerotic plaque. In terms of diabetes, Ly-6Chigh monocytosis is also associated with obesity-induced adipose tissue infiltration of Ly-6Chigh macrophages, which may contribute to the proinflammatory state associated with metabolic syndrome and diabetes. Direct connections among diabetic-associated vascular dysfunction, atherosclerosis, and monocyte-subsets in these animal models have not yet been made. However, in humans with diabetes and known vascular complications, the circulating levels of CD16+ monocytes are reduced. The importance of this finding is unclear as it relates to atherosclerosis pathogenesis in diabetes but continues to be pursued.

The role of specific monocyte subsets in diabetic macrovascular disease remains an active area of study. In murine models of T1DM, peritoneal macrophages elicited in response to thioglycolate injections demonstrate increased mRNA expression of proinflammatory mediators including TNF-α, IL-1β, prostaglandin- endoperoxide synthase 2 (TPGS2), and cyclooxygenase 2 (COX-2).[158,159] The effect on PTGS2 implicates long-chain fatty acids, and eicosanoids in particular, as potentially important sources of immunomodulation of monocytes and other vascular cells. Indeed, an important relationship between fatty acid signaling and monocyte activation exists in diabetes. TLRs, primitive pattern recognition receptors that activate proinflammatory

signal transduction cascades through NF-κB, can be activated by long-chain fatty acids. There is a twofold induction of cell surface TLR expression in peritoneal macrophages 6 weeks after induction of diabetes in mice, with lesser effects on TLR4 expression.[134] These peritoneal macrophages also demonstrate greater activation of NF-κB. Knockout of TLR2 abrogates almost all the augmentation in NF-κB activity. Similarly, levels of proinflammatory cytokines IL-1β, IL-6, MCP-1, and TNF-α are elevated in diabetic macrophages compared with nondiabetic cells, and TLR2 knockout significantly attenuates this induction. Altered PTGS2 expression along with the enzyme long-chain acyl-CoA synthetase (ACSL1) from mouse monocytes with T1DM correlates with increased levels of prostaglandin E_2 (PGE_2). In addition, $CD14^+$ monocytes from human patients with T1DM also demonstrated elevated levels of ACSL1 mRNA.[155] In M1 activated murine macrophages derived from bone marrow–derived monocytes, or human monocyte–derived macrophages (induced with LPS and interferon gamma [IFN-γ]), *ACSL1* gene expression is significantly induced as well. Notably, ACSL1 deficiency reduced the release of proinflammatory cytokines from LPS-stimulated macrophages isolated from diabetic mice.[158] ACSL1 deficiency in bone marrow reduced diabetes-associated atherosclerosis and monocyte accumulation in the vessel wall in low-density lipoprotein receptor (LDLr) deficient mice, suggesting that ACSL1 plays a specific role in monocyte recruitment and activation in experimental diabetic atherosclerosis. Whether this effect relates to altered PGE_2 production has not been proven, but it suggests that alterations in eicosanoid handling can influence diabetic atherosclerosis through changes in monocyte inflammatory activation.

Other drivers of inflammation and atherosclerosis relevant to diabetes are also under study. The activity of plasma and cell-surface enzymes, including Lp-PLA_2, can generate proinflammatory metabolites derived from oxidized phospholipids, a phenomenon that is being exploited as a candidate therapeutic target in prospective clinical trials.[160] Oxidatively modified lipoproteins and oxidized lipid constituents, and their impact on monocyte-macrophage biology and circulating antibodies, continue to received attention in general and also with regard to diabetes.[32] Autophagy—the process through which cells engulf and consumes themselves—has been invoked as a novel inflammatory mechanism in macrophages, influencing issues such as monocyte subtypes.[137,161] It is interesting to note that autophagy has also been raised as an important pathway in myocyte and cardiac myocyte biology. Another mechanism that has received increasing attention as a potential factor underlying diabetes and atherosclerosis is the notion of ER stress.[162–164] The ER is integral to the metabolism of proteins, lipids, and glucose, playing a part in lipoprotein secretion and other basic cellular processes. As such, the data identifying a role for ER stress in diabetes and atherosclerosis, with changes in apoptosis, inflammation, hepatic dysfunction, and other relevant settings, seem quite plausible and exciting, offering a new perspective on these complex issues.

Lymphocytes

Both B and T lymphocytes have been implicated in atherogenesis in both the absence and presence of diabetes. By immunohistochemistry, most lymphocytes in atherosclerotic plaque are $CD4^+$ cells, which have the capacity to differentiate along Th1 or Th2 lineages. Factors in the vessel wall including cytokine production by other lymphocytes, ECs, and macrophages dictate the differentiation fate of these cells. Lymphocyte differentiation has important effects on atherosclerotic plaque biology. Disruption of Th1 lineage reduces atherosclerosis in murine models of disease and has been generally associated with proatherosclerotic responses.[165,166] The role of Th2 cells is more controversial. In addition, smaller subsets of T cells including T regulatory cells (Tregs) and Th17 lymphocytes exert local control on plaque inflammation and plaque expansion. In diabetic patients, a lymphocytosis has been observed with expansion of a rare, proatherogenic $CD4^+$ CD28null T lymphocyte.[167] In patients with overt coronary syndromes and T2DM, the frequency of this lymphocyte population was 12.7% versus 3.8% in patients with acute coronary syndrome without T2DM. This effect was independently associated with glycosylated hemoglobin levels. Recent data demonstrate that the expansion of visceral fat is associated with a loss of local Treg cells. This highlights emerging data connecting changes in inflammatory cells and cardiometabolic issues.[168] The specific role of diabetes in lymphocyte activation during atherosclerosis lesion formation remains an active area of research.

Vascular Smooth Muscle

During the atherosclerotic process, VSMCs proliferate in the media and also migrate out of the media to the subintimal space, thereby enlarging the neointimal lesion. In human diabetes, VSMC reactivity is enhanced in isolated arteries exposed to norepinephrine or phenylephrine.[169] This effect correlates with reduced subplasmalemmal Ca^{2+}, which controls K^+ channels that regulate VSMC relaxation. VSMCs grown in culture medium supplemented with high glucose proliferate, migrate, hypertrophy, and produce extracellular matrix to a greater degree than cells grown in low-glucose media.[170,171] VSMCs isolated from the aortas of db/db mice—an established model of aggressive T2DM—demonstrate increased proinflammatory gene expression including MCP-1 and IL-6.[172,173] VSMCs from db/db animals migrated in response to platelet-derived growth factor (PDGF) to a significantly greater degree than VSMCs isolated from control, nondiabetic mice. These observations suggest that the diabetic environment "preactivates" VSMCs and predisposes these cells to invade the intima and further inflame the vessel wall.

Inflammation as a Therapeutic Target in Diabetic Atherosclerosis?

Although cell biologic approaches and animal models have provided key scientific insights into atherogenesis, ongoing efforts are directed toward translating these findings to human disease. The identification of stable, circulating biomarkers of inflammation has allowed investigators to test prospectively how indices of inflammation relate to atherosclerosis disease burden and clinical events, including responses to current agents and therapies under development.

PPARs have been extensively explored as therapeutic targets for improving both T2DM and diabetic atherosclerosis and provide an interesting example of the challenges in extending scientific advances to clinical benefit.[14,15] PPARs, members of the nuclear hormone receptor family, are ligand-activated transcription factors that control metabolic



gene expression in multiple tissues including adipose tissue, skeletal muscle, and liver. PPARs consist of PPAR-α, PPAR-γ, and PPAR-β/δ, different isotypes with unique profiles. The drugs constituting the class of thiazolidinediones (rosiglitazone, pioglitazone) were found to be potent insulin sensitizers by activating PPAR-γ, whereas fibrates lower hypertriglyceridemia and increase HDL by activating PPAR-α. It is interesting to note that these drugs were in clinical use before it was realized that these receptors were also expressed in vascular and immune cells. Subsequent studies established that PPARs were expressed in vascular and inflammatory cells, with a fairly extensive database demonstrating in general that PPAR activation limits inflammatory gene expression in ECs, VSMCs, and macrophages in vitro.[174–176] in vivo treatment of hypercholesterolemic mice with PPAR-α and PPAR-γ ligands also suppressed lesion formation in different models with and without diabetes.[177] PPAR effects correlated with alterations in macrophage foam cell formation in vitro. PPAR-δ has also been studied and implicated in these processes, although no PPAR-δ agonist has ever reached clinical approval.[178] Surrogate marker studies revealed that PPAR-γ and PPAR-α agonists could reduce hsCRP and decrease carotid intima-media thickness.[179] However, extending this relatively robust dataset to humans has yielded mixed results, as discussed elsewhere. Briefly, a meta-analysis of smaller studies with rosiglitazone suggested increased CV events.[180] A prospective, placebo-controlled study with pioglitazone—PRoACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events)—did demonstrate a 20% reduction in the secondary endpoint of major CV events in patients with diabetes.[181] A potentially misguided primary combined endpoint, which included typically unresponsive endpoints such as peripheral vascular disease intervention, was null, rendering this result more difficult to interpret. Important, pioglitazone did not seem to have higher risk of adverse events in this study. Similarly, fibrates as PPAR-α agonists have shown reduced CV events when used alone (gemfibrozil, Veterans Administration-HDL Intervention Trial "VA-HIT"), but there has been less definitive evidence in combination with statins, with perhaps the subgroup of patients with higher TG and lower HDL levels being the ones most likely to benefit.[182,183]

In terms of the vascular biology of diabetes, the PPAR experience offers potential insights and cautionary points. Prior data and studies that continue to emerge identify PPARs as critical regulators at the intersection of metabolism, inflammation, and atherosclerosis. A necessary distinction must be maintained between the biologic target and the therapeutic agent(s). Indeed, along these lines, some efforts continue to identify better approaches to modulating PPAR activity, including a dual PPAR-α–PPAR-γ agonist that is in a large, late-stage clinical trial in patients with acute coronary syndromes.[184] PPAR biology establishes several rationales for how different PPAR interacting agents might exert different biologic responses. If rosiglitazone does increase CV risk, one might also question the validity of surrogate markers, given the improvements observed with rosiglitazone. Perhaps the broader conclusion is that to appropriately evaluate agents with the potential to decrease CV events, definitive randomized clinical trials are needed. The experience with pioglitazone underscores the need for those trials to be carefully thought out, given that reversal of the primary and secondary endpoints in this trial, and a longer duration, may well have had a profound effect on the diabetes therapeutic landscape. Incretins (glucagon-like peptide-1 analogs), a new therapeutic modality for diabetes, also have direct effects on the vasculature.[185,186] Incretins are gastrointestinal hormones that increase insulin release from the pancreatic beta cell. As in the case of PPAR biology, the effects of incretins on CV outcomes remain an important issue of study.

In contrast to the complexities of the clinical experience with PPAR agents, HMG-CoA reductase inhibitors (statins) have been shown to clearly decrease CV risk in general as well as in patients with diabetes.[187] Several lines of evidence suggest that the benefits of statins may derive from anti-inflammatory effects, including some that may be independent of LDL lowering. Statins lower circulating hsCRP levels, as seen in the randomized, prospective primary and secondary CVD outcomes trials. Notably, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, the patients who benefited the most from high-dose atorvastatin therapy after acute coronary syndrome events were those individuals who achieved an LDL cholesterol level below 70 mg/dL and hsCRP level below 2.0 mg/L.[146] These clinical findings suggest that statins possess anti-inflammatory properties. In JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), 17,802 individuals without known CVD with average LDL cholesterol levels (<130 mg/dL, median 108 mg/dL) but hsCRP levels of 2 mg/L or higher were randomized to either placebo or rosuvastatin.[188] The study was terminated after only 3 years when the interim analysis revealed a 44% reduction in the primary CV end point. The treatment group had significant reductions in hsCRP (37%), but also reductions in LDL cholesterol (50%), making a definitive conclusion that the benefit derived from decreased inflammation difficult. Preclinical studies continue to suggest various mechanisms through which statins may decrease inflammation independent of LDL lowering, including changes in modification of proteins, induction of other targets such as the kruppel-like factor (KLF) transcription factors, and changes in mRNA stability, as reported for eNOS.

Given that statins appear to decrease both inflammation and LDL, interest has arisen in other therapies that might decrease inflammation in an LDL-neutral manner. Two large clinical trials are under way that will directly test the inflammation hypothesis: the Cardiovascular Inflammation Reduction Trial (CIRT; ClinicalTrials.gov identifier NCT01594333) and the Cardiovascular Risk Reduction Trial (CANTOS; ClinicalTrials.gov identifier NCT01327846).

The CIRT study, sponsored by the National Institutes of Health, is a multicenter, placebo-controlled trial in which patients with stable CAD on standard care (including statins) *and* metabolic syndrome or T2DM (n = 7000) who will be randomized to very low-dose methotrexate (15 to 20 mg weekly) with folate supplementation. Methotrexate was chosen because this U.S. Food and Drug Administration (FDA)–approved medication lowers hsCRP without affecting lipid levels, has an excellent safety profile, is well tolerated, and is inexpensive. Seven nonrandomized observational studies of patients with rheumatoid arthritis or psoriatic arthritis have demonstrated significant CV event reduction among individuals taking low-dose methotrexate. Notably, patients with chronic inflammatory conditions

such as lupus, rheumatoid arthritis, or inflammatory bowel disease are excluded from the trial. This study will directly test whether lowering inflammation can reduce recurrent CVD in patients with diabetes. Enrollment was scheduled to begin in October, 2012.

The CANTOS trial is a randomized, double-blind placebo-controlled, event-driven trial that will test whether quarterly, subcutaneous canakinumab, a human monoclonal antibody that neutralizes IL-1β action, can reduce the rates of recurrent MI, stroke, and CVD death. The fact that intracellular cholesterol crystals activate the Nod-like receptor protein 3 (NLRP3) inflammasome, a signaling pathway that generates the active form of IL-1β, along with other data, provided the rationale to study IL-1β inhibition in CVD.[189] IL-1β has been directly implicated in atherosclerosis and thrombosis. The study will enroll patients at least 30 days after MI with hsCRP levels of 2 mg/L or higher. Canakinumab has been shown to reduce inflammatory biomarkers including hsCRP. The results of both CIRT and CANTOS will provide crucial clinical trial data regarding whether targeting inflammation itself can alter the natural history of CVD in patients with metabolic disease or T2DM.

SUMMARY

Diabetes is a complex condition with a pathogenesis, like atherosclerosis, that involves multiple different inputs and likely represents distinct forms even beyond designations such as type 1 and type 2. The intricacies of this picture are evident in attempts to deconvolute the nature of the vascular biology of diabetic atherosclerosis—the factors that drive the disorder, determine outcomes, and, it is hoped, offer openings for interrupting the natural history. The challenges in understanding the molecular basis of the intersection of diabetes and atherosclerosis are legion, given overlapping issues between these two diseases: very long subclinical phases, a frequency in the population that sets up multiple confounding variables, shared mechanistic underpinnings, and cellular players such as adipocytes and macrophages with many similar characteristics. All of these issues combine with clinical experience to frame a fundamental question in this field: To what extent is diabetic atherosclerosis unique and distinct from atherosclerosis, or is it simply the same disease accelerated in the context of hyperglycemia and other factors? It is amazing that, despite intense efforts by many groups using different approaches over many years, this question remains unresolved. Clearly the issues considered here are important in diabetic atherosclerosis independent of whether they are unique to diabetes or not. Diabetic dyslipidemia is a central part of the diabetic picture, with all the key components of the arterial wall and the inflammatory system altered by interaction with the altered lipid metabolism of diabetes. Increased thrombogenicity clearly contributes to CV outcomes in patients with diabetes; the extent to which all aspects of coagulation are shifted in diabetes is impressive. Endothelial dysfunction is an early part of the disease even before diabetes or cardiovascular complications become apparent. Ultimately, the inflammatory responses generated by core elements of diabetes, such as hyperglycemia, elevated FFAs, and increased ROSs, may be pointing us in the direction we must head if we are to understand better diabetic atherosclerosis, identify the problems earlier, and further improve outcomes.

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11 Type 1 Diabetes and Associated Cardiovascular Risk and Disease



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Type 1 diabetes (T1D) is an autoimmune disease that causes destruction of the pancreatic beta cells, leading to absolute insulin deficiency (see also Chapter 3).[1] Type 2 diabetes (T2D), in contrast, is associated with obesity and is characterized by insulin resistance accompanied by an insufficient compensatory insulin secretory response (see also Chapter 1). T1D is not a rare condition; it affects an estimated 1.5 million people in the United States and 30 million worldwide.[2] T1D is the most common type of diabetes in youth, and by 18 years of age, 1/300 youth in the United States has T1D. However, T1D can also be diagnosed in adulthood; this accounts for 5% to 10% of all cases of diabetes worldwide.[3] The underlying differences in pathophysiology (autoimmune beta cell destruction in T1D compared with obesity accompanied by insulin resistance and beta cell dysfunction in T2D) are important considerations in the context of cardiovascular disease (CVD), cardiovascular mortality, and CVD risk factors in T1D as compared with T2D (see also Chapter 7). Another important consideration is that many people with T1D are under the age of 21 years, and the screening and treatment of CVD and its risk factors in children and adolescents with T1D are different from those in adults and less evidence based. (*Note:* The abbreviation *CVD* is used throughout the chapter unless a specific research study uses a different term.) In this chapter, the history, the scope of the problem of CVD in T1D including rates of disease, pathophysiology, risk factors, and treatment, and the outlook for CVD risk factors in T1D are reviewed. A recent consensus statement by the American Diabetes Association (ADA) and the American Heart Association (AHA) states that current recommendations for primary prevention of CVD in T2D appear appropriate for patients with T1D.[4] In addition, the ADA and AHA have recently published a joint scientific statement on T1D and CVD.[5]

HISTORY

T1D was a uniformly fatal disease before the discovery of insulin by Banting and Best in 1921.[6] The discovery of insulin and advances in care have transformed T1D from a subacute and fatal disease to a chronic disease with a high burden of daily individual care and serious acute (severe hypoglycemia and diabetic ketoacidosis [DKA]) and chronic (retinopathy, neuropathy, nephropathy, and CVD) complications. Achieving near-normal glucose control continues to be challenging because of limitations in compliance, medical care, and risk of hypoglycemia. In the past, patients with T1D were characterized by underinsulinization and a thin body habitus. However, increased emphasis has been placed on achieving near-normal glucose levels to prevent long-term microvascular and macrovascular complications since the publication of the findings from the Diabetes Control and Complications Trial (DCCT) in 1993 demonstrated the beneficial effects of intensive diabetes management on reduction of microvascular complications,[7] and then in 2005 the Epidemiology of Diabetes Interventions and Complications (EDIC) findings regarding macrovascular disease.[8] Diabetes care continues to improve based on such studies and advances in technology[9] including self-monitoring of blood glucose with home glucose meters and continuous glucose monitors,[10] continuous subcutaneous insulin infusions (insulin pumps),[11] insulin analogues with pharmacokinetic properties for basal and bolus administration,[12] and emerging artificial pancreas technology.[13–15]

MAGNITUDE OF THE CLINICAL PROBLEM OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES

Epidemiology of Type 1 Diabetes

Numerous multicenter epidemiologic studies such as the SEARCH for Diabetes in Youth study,[16,17] the EURODIAB study,[18,19] and the DIAMOND Project (World Health Organization Multinational Project for Childhood Diabetes)[20,21] report increases in T1D of 2% to 5% annually worldwide. The prevalence of T1D in youth younger than 20 years of age in the United States was estimated in the SEARCH study to be 2.28/1000 or over 150,000 youth with diabetes in the United States in 2001, the majority with T1D.[16] Worldwide rates of T1D vary as expected because of variation in autoimmune system genetics, exposure to environmental triggers, and differences in survival from diagnosis of T1D and lifespan postdiagnosis as a result of differences in health care systems. These rapid and sustained increases suggest a cause that is environmental or related to a gene-environment interaction instead of genetic shifts. Multiple ongoing studies are investigating the cause of T1D to identify targets for prevention.[22,23] Such studies are likely long-term projects, barring dramatic scientific breakthroughs, highlighting the need to improve cardiovascular health for people with T1D. (See also Chapter 3.)

Despite progress in clinical care and outcomes for patients with T1D, improvements in outcomes are urgently needed.[24,25] EURODIAB followed 28,887 children in 12 European countries and found a standardized mortality rate of 2.0.[26] CVD was emphasized as the predominant cause for premature mortality in people with T1D in a report from the United Kingdom with a hazard ratio of 3.7 for annual mortality for people with T1D compared with the general population (8.0 versus 2.4/100,000 person-years).[27] These data highlight the need for improved CVD health in patients with T1D; however, there is reason to believe that health outcomes for people more recently diagnosed with T1D will be superior, given that these data are based on historic outcomes before the widespread adoption of many of the current methods of care for T1D. For example, the Pittsburgh Epidemiology of Diabetes Complications (EDC) study findings reported that life expectancy for people with T1D diagnosed from 1965 to 1980 was 15 years longer than for those diagnosed from 1950 to 1964.[28] The life expectancy of patients with T1D continues to improve[29,30]; however, the average life expectancy remains reduced by approximately 20 years relative to the general population.[31]

Rates of Cardiovascular Disease in Type 1 Diabetes

Increased rates of coronary heart disease (CHD) and death from CHD in T1D were reported in the 1970s.[32,33] The Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality study reported a 10-fold higher rate of CHD mortality associated with type 1 diabetes mellitus (T1DM) as compared with individuals without diabetes in the United States,[34] similar to a study from the Joslin Diabetes Clinic that reported a six-times higher rate of CHD by 55 years of age in people with T1D as compared with controls with use of Framingham study data.[35] Among people diagnosed with diabetes who were younger than 30 years of age, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported a standardized mortality rate of 9.1 for men and 13.5 for women.[36] More recent data from 23,751 people with insulin-treated diabetes diagnosed before 30 years of age continue to show increased standardized mortality rates for ischemic heart disease, with a markedly increased rate in women, who had rates of death from heart disease that were similar to those in men younger than 40 years with diabetes.[37] The Pittsburgh EDC study has followed people with T1D (diagnosed from 1950 to 1980) for incidence of coronary artery disease (CAD) and has not detected decreases in CAD over time (stratified for T1D durations of 20, 25, and 30 years) despite decreases in mortality, neuropathy, and renal failure.[38] Data from the large (N = 21,789) population-based Scottish Registry Linkage Study reported that the age-adjusted incidence rate ratio for CVD and mortality in patients with T1D compared with those without diabetes was 3.0 (95% confidence interval [CI] 2.4-3.8) for women and 2.3 (95% CI 2.0-2.7) for men. Moreover, the incidence rate ratio for all-cause mortality was elevated similarly for both women 2.7 (95% CI 2.2-3.4) and men 2.6 (95% CI 2.2-3.0).[39] The authors concluded that despite improvement in risks for CVD and mortality for people with T1D, these rates continue to be higher than in the nondiabetic population and that CVD risk factor management needs to be improved, especially methods to achieve better glucose control.

Multiple risk factors for CVD in T1D exist, with glucose control considered to be the most likely factor accounting for increased risk as compared with nondiabetic controls. Despite a relatively small number of events compared with studies in patients with T2D, the DCCT and EDIC trials reported a 57% reduction in CVD in the intensively managed as compared with the conventional arm after 17 years of follow-up.[8] Similarly, the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, a longitudinal study of atherosclerosis in 1416 young adults with and without T1D, reported an association of HbA1c with progression of coronary artery calcification (CAC), an intermediate marker of coronary atherosclerosis.[40] However, data from epidemiologic studies on glucose control in T1D and CVD are inconclusive and have been the subject of review.[41] The ADA recommends an ABC approach to CVD: In addition to glucose control (HbA1c or A), blood pressure (B) and cholesterol (C) are emphasized.[42] Other modifiable CVD risk factors for people with T1D include kidney disease, obesity, insulin resistance, inflammation, and lifestyle factors such as smoking, diet, and exercise. Nonmodifiable CVD risk factors include genetics and family history and T1D duration. These are reviewed later in the chapter.

Specific Considerations for Cardiovascular Disease in Type 1 Diabetes: Age and Comparison with Type 2 Diabetes

T1D is frequently diagnosed in childhood, which includes the challenges associated with the physiologic changes of puberty. It has been well established by studies such as the Bogalusa Heart Study,[43] the Muscatine study,[44] the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study,[45] and the Young Finns Study[46] that atherosclerosis begins in youth and that the extent of atherosclerosis is associated with the presence and extent of CVD risk factors. These studies also demonstrate tracking of CVD risk factors from childhood into adulthood and argue for earlier attention to CVD risk.[47] Therefore, primary prevention of CVD and attention to CVD risk factors has gained increased attention in the past decade. For example, the ADA,[48] the AHA,[49] the American Academy of Pediatrics (AAP),[50] and the International Society for Pediatric and Adolescent Diabetes (ISPAD)[51] have all published guidelines for CVD health in youth with T1D; **Figure 11-1** shows the AHA guidelines for risk stratification and treatment. One such example of these includes thresholds for pharmacologic treatment of dyslipidemia and goals for lipids, although these are not based on randomized trials assessing CVD outcomes. Age- and gender-specific normal and abnormal values linked to the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) lipoprotein thresholds have also been calculated using National Health and Nutrition Examination Survey (NHANES) data[52] that recognize physiologic variations seen with pubertal development. Additional considerations for CVD risk factors in the pediatric diabetes population that have raised concerns about treatment include costs, lack of outcome data, potential life-long treatment, and adverse effects. Arguments for treatment include the tracking of CVD risk factors levels from childhood into adulthood, extensive data in adults on the benefits of lowering CVD risk factors to prevent CVD in adults with T1D, and the association of CVD risk factors with intermediate markers of atherosclerosis (**Table 11-1**).[53]

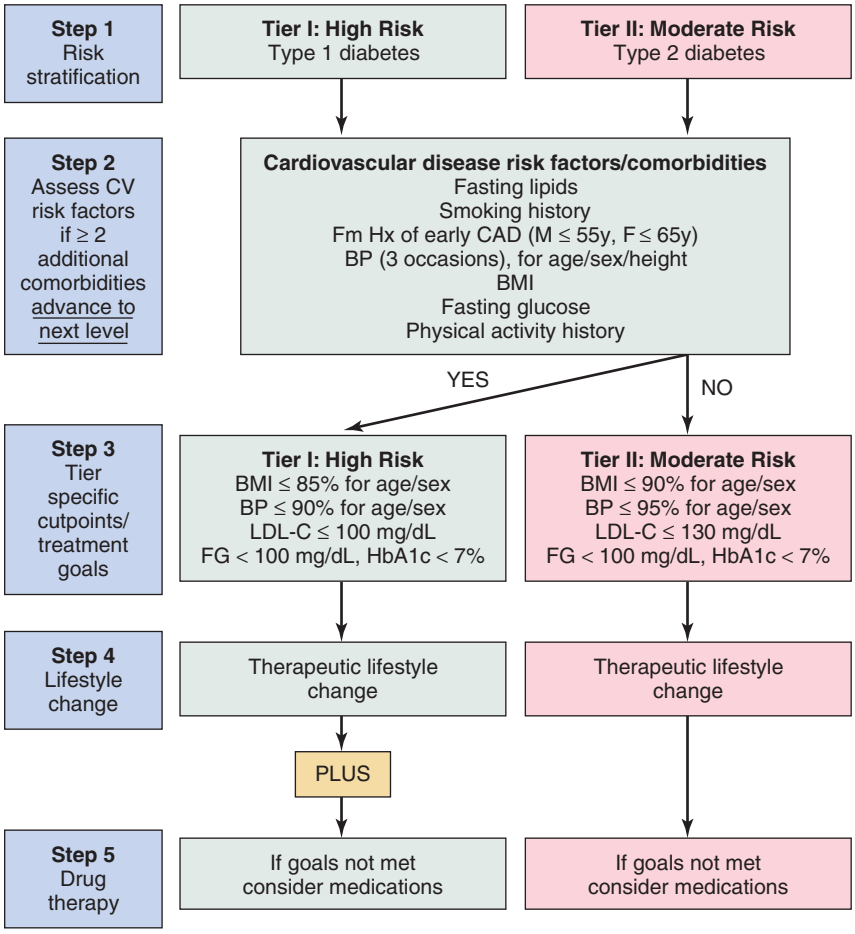


FIGURE 11-1 American Heart Association guidelines for risk stratification and treatment in youth with diabetes. *(Modified from Maahs DM, Wadwa RP, Bishop F, et al: Dyslipidemia in youth with diabetes: to treat or not to treat?* J Pediatr *153:458-465, 2008.)*

In adults, recommendations for CVD risk modification in T1D continue to evolve. For adults, NCEP-ATP III considers diabetes to be a CHD risk equivalent and therefore uses goals for low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) of below 100 mg/dL (optional <70) and below 130 mg/dL (optional <100), respectively. The most recent joint position statement from the ADA and AHA does not distinguish CVD risk between T1D and T2D, citing a lack of evidence to do so.[4] As additional data accumulate, specific recommendations for adults with T1D will evolve. The recent ADA-AHA Scientific Statement on CVD in T1D summarizes the relative association of specific CVD risk factors and CVD events in T1D versus T2D (**Table 11-2**),[5] including that women with T1D are equally affected as men with T1D, unlike in T2D, in which men have increased rates of CVD.

Cardiovascular Disease Pathophysiology in Type 1 Diabetes

The recent ADA-AHA Scientific Statement calls for additional research into the differences in the atherosclerotic process between T1D and T2D,[5] although a summary of available data follows. A small study found similar CAC scores in T1D and T2D patients, but more obstructive lesions, more noncalcified lesions, and more lesions in general in T2D compared with T1D patients.[54] An earlier small study reported less atherosclerosis in T1D versus T2D patients.[55] Angiographic studies suggest more severe stenoses and more extensive involvement in people with T1D compared with those without diabetes,[56] and another reported more severe distal disease with an approximately four times higher burden of atherosclerosis.[57] An autopsy study in T1D reported plaques were soft and fibrous with a more concentric location.[58] These studies were generally small and may not be representative of the T1D population. The nature of plaque in T1D is less well studied than in T2D, but the plaque may be more calcified and fibrotic and contain less lipid. More studies using techniques such as intravascular ultrasound and postmortem studies are needed.

CARDIOVASCULAR DISEASE RISK FACTORS IN TYPE 1 DIABETES

Modifiable Risk Factors: ABCs

A: A1c (or Hemoglobin A1c and Glucose Control)

As reviewed earlier, outcomes in T1D continue to improve as care for T1D improves. Although data suggest that the mean hemoglobin A1c (HbA1c) level has improved post-DCCT, these improvements are not as rapid as clinicians or patients wish. For example, the Diabetes Patienten Verlaufsdokumentation (DPV) study in children and adolescents with T1D in Germany and Austria (N = 30,708) reported a decrease in HbA1c of 0.038%/year from 8.7% in 1995 to 8.1% in 2009.[59] Although encouraging, at this pace of improvement mean HbA1c will not reach the adolescent goal of 7.5% for many years to come. Similarly, large studies from Australia,[60,61] Norway,[62] and Denmark[63] support improvement in HbA1c in the past decades. In the United States, the Type 1 Diabetes Exchange

TABLE 11-1 Pros and Cons of Pharmacologic Treatment of Cardiovascular Disease (CVD) Risk Factors in Patients with Type 1 Diabetes

PROS	CONS
CVD risk factors extend into adulthood and likely will remain abnormal.	Wait until adulthood to treat CVD risk factors for the following reasons: The 10-year risk of a CVD event is unknown at the present time. Refer patient to an adulthood endocrinologist once the patient is 18 years old for treatment at that time.
Adolescent risk factors predict surrogate markers of cardiovascular disease (CIMT) in adults (Young Finns, Bogalusa).	Some data suggest that regression, or at least slowing of progression, of atherosclerosis with aggressive treatment is possible in adults.
CVD risk factors are associated with atherosclerosis in childhood.	There are no data that treatment in youth will reduce long-term CVD complications.
CVD risk factors are an important microvascular and macrovascular risk factors.	*Primum non nocere:* There are potential adverse events from pharmacologic treatment. There is potential teratogenicity for adolescent girls.
Type 1 diabetes (T1D) is considered a CVD risk factor equivalent in adults.	Cost: The number needed to treat to prevent CVD events cannot be calculated. Many years of treatment are required, with potential for life-time treatment.
Earlier T1D onset results in a longer T1D disease burden and potential adverse "vasculo-metabolic memory" and an increased "area under the curve" for CVD risk factors.	There is some measurement variability with regression to the mean of CVD risk factors, although they tend to track as high or normal.
There is a long-term elevated risk of CVD in youth with CVD risk factors (PDAY, Young Finns, Bogalusa).	There are no outcome data and no safety data in youth with T1D.
There is a preponderance of data regarding lowering CVD risk in adults; why wait?	

CIMT = Carotid intima-media thickness; PDAY = Pathobiological Determinants of Atherosclerosis in Youth study.
Data from Maahs DM, Wadwa RP, Bishop F, et al: Dyslipidemia in youth with diabetes: to treat or not to treat? *J Pediatr* 153:458-465, 2008.)

TABLE 11-2 Relative Association between Specific Cardiovascular Risk Factors and CVD Events in T1D versus T2D (Range 0 To +++)

	T1DM	T2DM
Hypertension	+++	++
Cigarette smoke	++	++
Inflammation	+	++
High LDL-C	+	++
Low HDL-C	0,+	++
TG	No data	++
Microalbuminuria	+++	+++
Insulin resistance	+	+++
Poor glycemic control	++	+++

TG = Triglyceride(s); + = strong association; ++ = stronger association; +++ = strongest association.
Data from de Ferranti SD: Type 1 diabetes mellitus and cardiovascular disease, *Circulation*. In press.

reported only 27% of children younger than 13 years and 23% of 13- to 20-year-olds met the ISPAD HbA1c target of 7.5%.[64] In adults with T1D, the EDC study reported decreases in HbA1c from 9.0% to 8.5% to 8.3% from the mid-1980s to the mid-2000s (**Table 11-3**). The Type 1 Diabetes Exchange reported that the mean HbA1c level in T1D exceeds the ADA goal in all age groups (**Fig. 11-2**). These data on HbA1c are important because, as mentioned previously, the DCCT-EDIC study demonstrated that intensive diabetes management (with resultant HbA1c contrast of 7.3% in the intensive arm versus 9.1% in the conventional arm) resulted in a 57% reduction in CVD events,[8] although there were relatively few events. Similarly, a meta-analysis found a lower relative risk for macrovascular events (0.38, 95% CI 0.26-0.56) for intensive versus conventional therapy.[65] These data are consistent with other DCCT-EDIC data on intensive management (and lower HbA1c), with more favorable effects on intermediate markers of CVD such as carotid intima-media wall thickness (CIMT)[66] and CAC.[67] However, perhaps because of methodologic issues, HbA1c has not consistently been associated with CVD in epidemiologic studies.[41] For example, the EURODIAB study did not find an association of HbA1c with CHD,[68] nor did the Pittsburgh EDC study in earlier investigations,[69,70] but did in a later study in which glucose control was more strongly associated with CAD mortality than morbidity.[71] Similarly, in the WESDR study, HbA1c was associated with CVD mortality but not myocardial infarction.[72,73] A large Swedish database (N = 7454) reported a 30% increased hazard ratio for CAD per 1% increase in HbA1c.[74]

With improved glucose control, there is a concern that this will lead not only to increases in hypoglycemia and weight, but an altered lipoprotein profile as seen in a subset of patients in the DCCT.[75] There are data to suggest that properly focused intensification of glucose control can be achieved without increases in weight,[76] and such efforts are important to avoid the unwanted effects of weight gain on insulin resistance and lipids.

B: Blood Pressure or Hypertension

Hypertension is a strong risk factor for CVD. In T1D, hypertension is related to increased risk of both microvascular[77–79] and macrovascular disease.[70,80] In both youth and adults, the prevalence of hypertension is higher in people with T1D as compared with those without diabetes. Data from the Pittsburgh EDC study on the predictors of major outcomes in T1D showed that the importance of glucose control on outcomes diminished over time (perhaps because of improved control), but hypertension continued to be a strong predictor of CVD, suggesting the importance of blood pressure control on outcomes in T1D.[81] Few findings from pharmacologic intervention trials regarding the ideal threshold for blood pressure in T1D have been published, and angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are most commonly used,[82] consistent with professional society recommendations.[42] In a small randomized clinical trial (N = 54), no difference was reported in blood pressure lowering or glomerular filtration rate (GFR) between the enalapril or nifedipine arms.[83]

One important consideration in youth is that hypertension is defined based on age and gender percentiles. In youth with T1D, estimates of hypertension prevalence range from 4% to 8%.[84–87] Predictors of blood pressure in youth with diabetes include glucose control,[88] obesity,[89] and diet.[90] Of note, treatment of hypertension in youth with diabetes is reported to be low, with only 1.5% and 2.1% of youth reporting treatment

TABLE 11-3 Clinical Characteristics of the DCCT/EDIC and EDC Cohorts

	Conventional						*Intensive*		
	DCCT		**EDIC**		**EDC**		**DCCT**		**EDIC**
Characteristic	Baseline (1983-1989) (N = 730)	Closeout (1993) (N=723)	Year 12 (2005) (N=606)	Baseline (1986-1988) (N=161)	Year 10 (1996) (N=105)	Year 18 (2006) (N=88)	Baseline (1983-1989) (N=711)	Closeout (1993) (N=698)	Year 12 (2005) (N=620)
Age, mean (SD), years	27 (7)	33 (7)	46 (7)	20 (4)	31 (4)	40 (4)	27 (7)	34 (7)	46 (7)
Duration, mean (SD), years	5 (4)	12 (5)	24 (5)	11 (2)	21 (2)	30 (2)	6 (4)	12 (5)	25 (5)
BMI, mean (SD)	24 (3)	25 (3)	28 (5)	24 (3)	26 (4)	28 (5)	23 (3)	27 (4)	28 (5)
BMI ≥30, %	2	6	28	3	1	27	1	19	31
Current smoker, %	18	20	12	20	17	15	19	20	15
HbAtc % (SD)	8.9 (1.6)	9.1 (1.5)	7.7 (1.2)	9.0 (1.7)	8.5 (1.4)	8.3 (1.8)	8.9 (1.6)	7.4 (1.1)	7.8 (1.2)

BMI = Body mass index; SD = standard deviation.
Data from Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group; Nathan DM, Zinman B, Cleary PA, et al: Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983-2005), *Arch Intern Med* 169:1307-1316, 2009.

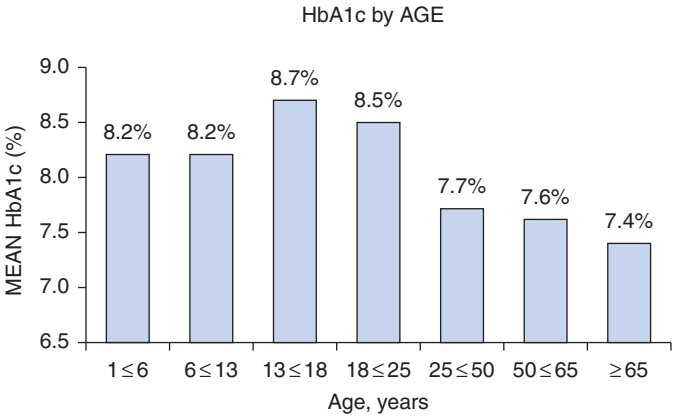


FIGURE 11-2 Mean HbA1c in T1D Exchange by age.

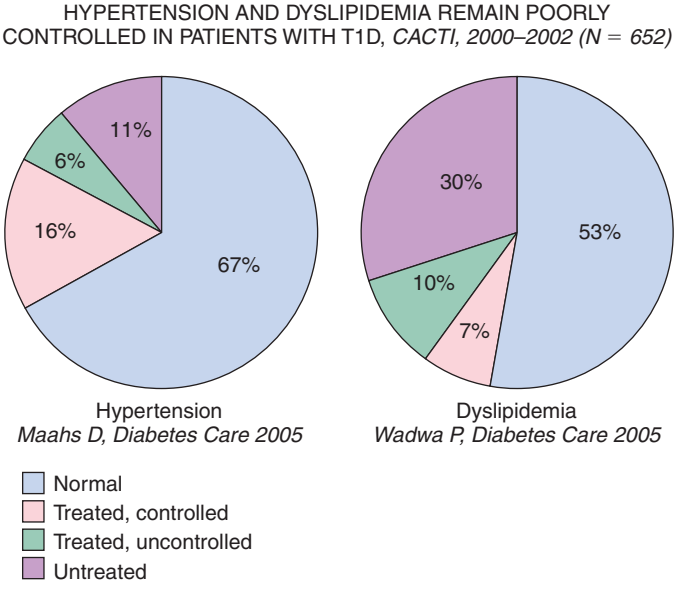


FIGURE 11-3 Hypertension and dyslipidemia remain poorly controlled in patients with T1D, CACTI, 2000-2002 (N = 652). *(Data from Maahs DM, Kinney GL, Wadwa P, et al: Hypertension prevalence, awareness, treatment, and control in an adult type 1 diabetes population and a comparable general population,* Diabetes Care *28:301-306, 2005; and Wadwa RP, Kinney GL, Maahs DM, et al: Awareness and treatment of dyslipidemia in young adults with type 1 diabetes,* Diabetes Care *28:1051-1056, 2005.)*

with blood pressure–lowering medications in the SEARCH[86] and DPV[87] studies, despite 5.9% and 8.1% prevalence of hypertension in the T1D subjects in each study. In addition to measurement of blood pressure during office visits, 24-hour ambulatory blood pressure has been used to detect reduced nocturnal dipping, which has been associated with development of microalbuminuria.[91]

In adults, the CACTI study reported higher rates of hypertension prevalence (43% versus 15%, $P < 0.0001$), awareness of hypertension, treatment, and control in adults with T1D than in those without diabetes (**Fig. 11-3**).[82] These observations suggest that adults with T1D are more likely to be hypertensive than individuals without diabetes, but also to be more aware of the diagnosis and to be treated, although only 42% of the T1D adults achieved the JNC 7 goal of below 130/80 mm Hg.[92] Similarly, the EURODIAB study reported that less than 50% of T1D adults with hypertension were treated to goal.[93] The most recent ADA recommendations suggest that blood pressure should be measured routinely at each visit and that patients with hypertension should be treated to a goal of less than 140/80 mm Hg, although lower targets may be appropriate.[42] Patients with a blood pressure exceeding 120/80 mm Hg are recommended to make healthy lifestyle changes including weight loss, dietary changes (such as use of the DASH diet [Dietary Approaches to Stop Hypertension]), moderation of alcohol intake, and increased physical activity. ACE inhibitors or ARBs are recommended as first-line pharmacologic treatment, and multiple medications are often required to achieve control.

C: Cholesterol (Dyslipidemia)

Data from the DCCT[94] and others such as the CACTI study[95] indicate that adults with well-controlled T1D have fasting lipid profiles similar to or even less atherogenic than nondiabetic controls. As in the nondiabetic population, dyslipidemia is considered an important risk factor for CVD in T1D, although the frequency of dyslipidemia does not explain the increased rates of CVD in T1D. Data from the EDC study suggest that LDL-C levels below 100 mg/dL are associated with increased CVD risk[96] and that the usual inverse association of HDL-C to CVD risk is seen in men but not in women, who had little association between HDL-C levels above the 50- to 60-mg/dL range and CVD risk.[97] In

addition, rates of statin treatment have increased in adults with T1D over time. For example, the CACTI study reported statin use increased from 17% to 32% to 46% of the cohort over three study visits from 2000 to 2006.[98] Longitudinal data from the DCCT-EDIC, the EDC, and the Scottish Care Information–Diabetes Collaboration database studies also show a similar increase in the use of statins.[39,99] However, despite this increase in statin use, 39% of people with T1D who were older than 40 years in the Scottish study were not treated with a statin. Moreover, the trials with statins have included too few patients with T1D to be definitive, but the outcomes suggest benefit with regard to major CVD events.[100] One of the potential effects of more intensive glucose control is increased weight gain with associated deleterious effects on the lipid panel[75,101]; however, the increased use of statins in T1D may explain improved lipid profiles over time.

Risk factors for elevated lipids in T1D include male gender, older age, increased waist circumference and visceral fat, and higher HbA1c[98] as well as renal disease (proteinuria and decreased GFR) and autoimmune thyroid disease. In longitudinal analyses of epidemiologic data in both children and adults, change in HbA1c was associated with change in lipids; however, these associations are relatively modest—for example, a 4-mg/dL change in LDL-C for every 1% change in HbA1c[98,102]—a much weaker effect than would be expected from a statin. This suggests that although glucose control is the cornerstone of care, it may be insufficient to achieve lipid targets in most people with T1D (**Fig. 11-4**).

Excellent reviews of the pathophysiology of lipid disorders in T1D have been published historically[103] and more recently by Verges.[104] In general, abnormalities of lipoproteins in T1D can be classified in the context of the underlying glucose control, which is a function of matching exogenous insulin delivery to maintain near euglycemia (or the failure to do so) and how this alters normal lipid and lipoprotein physiology. T1D lipid pathophysiology can be considered in the categories of untreated T1D with extreme insulin deficiency such as seen in DKA in contrast to treated T1D with varying degrees of glucose control and insulin resistance.

Since publication of the 2003 ADA statement on Management of Dyslipidemia in Children and Adolescents with Diabetes,[105] data have accumulated indicating dyslipidemia is common in youth with T1D. A retrospective cross-sectional analysis of 682 youth with T1D younger than 21 years revealed that 18.6% had total cholesterol (TC) exceeding 200 mg/dL or HDL-C below 35 mg/dL,[106] with longitudinal analysis in the same cohort indicating sustained abnormalities over time with only 6% being treated with a lipid-lowering medication.[107] The DPV study (N = 27,358) in Germany and Austria reported dyslipidemia (defined as TC above 200 mg/dL, LDL-C above 130 mg/dL, or HDL-C below 35 mg/dL) in 29% of the participants younger than 26 years with increasing rates in older age categories.[87] Similarly, only 0.4% in this study received lipid-lowering medications. In the SEARCH study of youth with T1D (N = 2165), the prevalence of LDL-C above 160, above 130, and above 100 mg/dL was 3%, 14%, and 48%, respectively.[108] Among these participants, only 1% were on lipid-lowering medications, indicating that in the years after the 2003 ADA statement,[105] few pediatric endocrinologists or primary care providers were treating elevated LDL-C pharmacologically as recommended by the ADA. However, these data may not reflect more current practice in pediatrics. More recently, data from the Type 1 Diabetes Exchange report similar rates of dyslipidemia among participants with available data; 95% and 86% met ADA (HDL-C of 35 mg/dL or higher) and ISPAD (HDL-C above 1.1 mmol/L or 41 mg/dL) HDL-C targets, and 35% and 10% exceeded LDL-C (100 mg/dL) and TG (150 mg/dL) targets.[64]

The ADA recommends screening for dyslipidemia in children with T1D after glucose control has been established in children older than 2 years if there is a family history of hypercholesterolemia or a CVD event before age 55 years or if the history is unknown (**Table 11-4**). If family history is not a concern, then screening is recommended at puberty; if findings are normal, then screening is repeated every 5 years,[42] similar to the AHA guidelines (see **Fig. 11-1**).[110] In children with diabetes, goals for lipids include LDL-C below 100 mg/dL, HDL-C above 35 mg/dL, and TG below 150 mg/dL. Similar cut points are used for AHA[110] and ISPAD.[51] For adults, NCEP-ATP III considers diabetes (without distinction between T1D or T2D) to be a CHD risk equivalent and therefore uses goals for LDL-C and non–HDL-C of below 100 (optional <70) and below 130 (optional <100) mg/dL, respectively.

Additional considerations in a patient with T1D include the risk of hypoglycemia while the patient is in the fasted state, when fasting for the purpose of lipid profiling. It has been suggested that a nonfasting sample for analysis of lipids may be an effective screening tool for most people with T1D.[53] Data from the DPV registry (N = 29,979) suggest that fasting status had a minimal effect on TC, LDL-C, and HDL-C.[111] Therefore it seems reasonable to screen for dyslipidemia in people with T1D with a nonfasting sample, with the caveat that a repeat evaluation may be required to better delineate lipid health.

An additional factor in treatment of dyslipidemia as with other CVD risk factors in T1D will be continued advances in pharmacologic therapy. Statins have been introduced, and the accumulation of safety and efficacy data as well as a decrease in price have led to their increased use. Data on the use of lipid-lowering medications in T1D are more limited than in T2D; specifically, the Cholesterol Treatment Trialists' Collaborators reported a 21% proportional reduction in major vascular events per mmol/L reduction

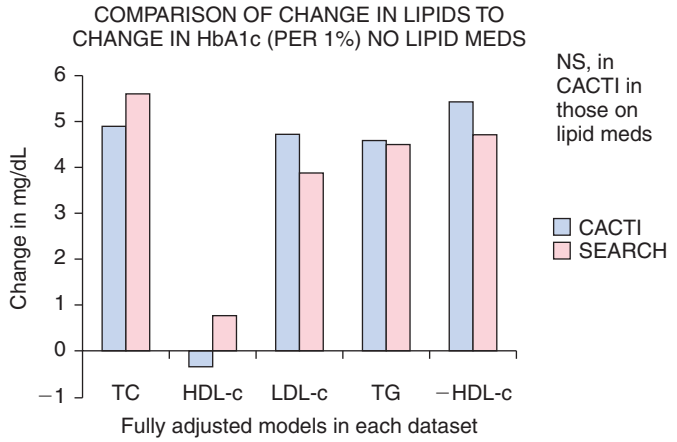


FIGURE 11-4 Association of change in lipids/1% change in HbA1c in CACTI and SEARCH. *(Data from Maahs DM, Ogden LG, Dabelea D, et al: Association of glycaemia with lipids in adults with type 1 diabetes: modification by dyslipidaemia medication,* Diabetologia *53:2518-2525, 2010; and Maahs DM, Dabelea D, D'Agostino RB Jr, et al: Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes,* J Pediatr *162:101-107, 2013.)*

TABLE 11-4 ADA Recommendations for Lipid Screening and Management in Youth with Diabetes

	T1D	T2D
Initial screening age (after glycemic control has been achieved)	Over 2 years at diagnosis if unknown or with a positive family history; otherwise at 12 years (puberty)	At diagnosis
Rescreening if lipid levels are normal	5 years	2 years
Optimal concentrations	LDL-C: <100 mg/dL	LDL-C: <100 mg/dL
	HDL-C: >35 mg/dL	HDL-C: >35 mg/dL
	Triglycerides: <150 mg/dL	Triglycerides: <150 mg/dL
	Goal LDL-C: <100 mg/dL	Goal LDL-C: <100 mg/dL
Management of Elevated LDL-C		
Initial therapy	Glycemic control, MNT, physical activity, weight control, tobacco cessation	Glycemic control, MNT, physical activity, weight control, tobacco cessation
After 3 to 6 months	LDL-C >160 mg/dL: begin medication	LDL-C >160 mg/dL: begin medication
	LDL-C 130-159 mg/dL: recommended after MNT failure based on other CVD risk factors	LDL-C: 130-159 mg/dL: recommended after MNT failure based on other CVD risk factors
	Pregnancy counseling if statin is started	Pregnancy counseling if statin is started

MNT = Medical nutritional therapy.
Data from Maahs DM, Wadwa RP, Bishop F, et al: Dyslipidemia in youth with diabetes: to treat or not to treat? *J Pediatr* 153:458-465; 2008.

(38.6 mg/dL reduction) in LDL-C in people with T1D (n = 1466 in a meta-analysis from 14 randomized statin trials).[100] However, there is some concern that adequate documentation of T1D was lacking.

For initial treatment of dyslipidemia, the ADA recommends optimization of glucose control and medical nutritional therapy (MNT), basically a diet that includes multiple servings of fruits and vegetables, whole grains, lean poultry, and fish and contains limited amounts of saturated fat. Statin therapy is recommended for patients with LDL-C above 160 mg/dL, or above 130 mg/dL in the presence of one or more CVD risk factors after MNT and lifestyle changes in patients with T1D younger than 10 years.[42] Presently, the ADA considers an adult T1D patient statin eligible unless he or she has LDL-C below 100 mg/dL and/or is pregnant, nursing, or attempting to conceive.[42] At what age the statin should be started or given to T1D patients who have LDL-C below 100 mg/dL remains an uncertainty.[53]

Other Cardiovascular Disease Risk Factors

Kidney Disease

With advances in clinical care, people with T1D are living longer and healthier lives, which highlights the need for refinement of care for chronic comorbidities such as CVD and its risk factors. Historically in the 1970s and 1980s, diabetic renal disease (most commonly with proteinuria) was associated with rapid progression to death, frequently as a result of CVD.[112,113] With advances in diabetes care including improved glucose and blood pressure control, patients with T1D without baseline diabetic kidney disease (either estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or microalbuminuria) had similar mortality outcomes to those of nondiabetic patients over 7 years in the Finnish Diabetic Nephropathy Study (FinnDiane)[114] and over 20 years in the Pittsburgh EDC study.[115] The CACTI study found increased CAC progression in a stepwise manner with increasing albumin-to-creatinine ratios (ACR) and decreasing eGFRs (**Fig. 11-5A, B**). In contrast, even in the absence of early diabetic kidney disease, people with T1D had increased odds of progression of CAC over 6 years compared with those without diabetes.[116] Whether increases in CAC predict an earlier development of CVD events and/or related mortality in people with T1D remains to be shown.

Given the well-established association of kidney disease to CVD and mortality in T1D, screening for elevated urinary ACR is recommended annually in adolescents and adults and eGFR is recommended in adults with T1D.[42] Rates of microalbuminuria in research studies in youth with T1D have ranged from 5% to 10% in recent decades,[117–119] with reports of the clinical diagnosis of microalbuminuria of 4.3% and 3.8% from the large DPV study[120] (n = 27,805) and the Type 1 Diabetes Exchange (N = 6784),[121] respectively. Of note, in the Type 1 Diabetes Exchange, only 41% of adolescents with the diagnosis of microalbuminuria reported ACE inhibitor or ARB treatment. Prevention and treatment of early diabetic kidney disease remains a clinical challenge in T1D with important implications for CVD prevention.

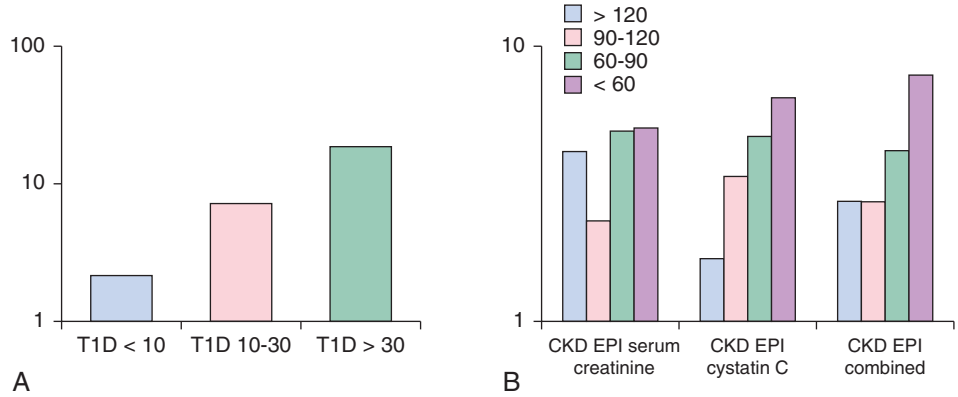


FIGURE 11-5 Odds ratio for CAC progression (CACp) by ACR and eGFR status. A, Odds ratio for CACp by ACR status. **B,** Odds ratio for CACp by eGFR category (patients without diabetes are reference group with odds ratio of 1) in CACTI. *(Modified from Maahs D, Jalal D, Chonchol M, et al: Impaired renal function further increases odds of 6 year coronary artery calcification progression in adults with type 1 diabetes: the CACTI Study,* Diabetes Care *36:2607-2614, 2013.)*

Obesity and Insulin Resistance

Rates of obesity in people with T1D in the United States are now similar to the increased rates of obesity in the U.S. general population. The average body mass index (BMI) has increased in the past two decades in the DCCT-EDIC and the Pittsburgh EDC studies, likely because of aging of the patients, more intensive glucose control, and the increasing prevalence of obesity in the United States in general (see **Table 11-3**). Similarly, in children with diabetes, an increased prevalence of obesity has been reported over the past decade.[122] The SEARCH study found either overweight or obesity in 37% of female patients and 32% of male patients with T1D.[123] Increased weight gain with intensive glucose control can be an impediment to reaching HbA1c goals and could worsen some CVD risk factors. Obesity also increases insulin resistance both in people without diabetes[124,125] and in those with T1D, both historically[126,127] and in the post-DCCT era with achievement of tighter glucose control.[128,129]

In addition to poor glucose control, insulin resistance caused by increasing adiposity and associated peripheral hyperinsulinemia can result in a lipid profile similar to that seen in the metabolic syndrome or T2D with elevated TG and decreased HDL-C. Studies have evaluated the addition of metformin to insulin to improve insulin resistance in people with T1D with mixed effects on HbA1c but some improvement in lipids.[130] The role of insulin sensitizers in T1D and the potential benefits with regard to CVD risk factors require further evaluation.[131] Recent data from the DCCT-EDIC study indicate that excess weight gain in DCCT was associated with sustained increases in central obesity, insulin resistance, dyslipidemia, and blood pressure and more atherosclerosis as measured by CAC and CIMT.[132]

With current methods of intensive glucose control, insulin is delivered subcutaneously and leads to peripheral hyperinsulinemia,[133] but research is ongoing regarding intraperitoneal insulin infusion with implantable insulin pumps that more closely mimic physiologic insulin delivery. Such devices have the potential to achieve more physiologic control of T1D and may have beneficial effects on CVD risk factors.[134,135]

Inflammation

Inflammation is a fundamental factor in the cause of atherosclerosis (see also Chapter 10)[136] and is implicated in the pathophysiologic process of the development of T1D (see also Chapter 3).[137,138] Higher levels of interleukin 6 (IL-6) and fibrinogen were reported in children and adolescents with T1D as compared with normal-weight controls in the SEARCH for Diabetes in Youth study.[139] Also, C-reactive protein (CRP) was higher in the top quartiles of HbA1c, and inflammation was associated with dyslipidemia. Wadwa and colleagues have reported that soluble IL-2 receptor, a marker of T cell activation, was associated with progression of CAC in people with (and without) T1D in the CACTI study.[140] In addition, subjects with T1D exhibit elevated levels of inflammatory endothelial markers such as sICAM, sVCAM, sE-selectin, suggesting endothelial dysfunction.[141] More recently, Alman and colleagues reported that a broad panel of inflammatory markers (with sTNFR2, sIL-2R, IL-18, sIL-1RA, and tumor necrosis factor α [TNF-α] being the most strongly loaded in the principal component analysis) was associated with progression of CAC in the CACTI cohort.[142] In addition, recent data suggest that a postinfarction autoimmune syndrome (myocarditis) may contribute to worse postmyocardial infarction outcomes in people with T1D.[143,144] Additional data are required on the mechanisms of inflammation in CVD in T1D, whether it differs from findings in individuals without diabetes, and what therapeutic targets exist to reduce CVD.

Lifestyle Modification: Smoking, Diet, and Exercise

Smoking prevention, healthy diet, and increasing exercise are standard lifestyle modifications for people with T1D with well-documented health benefits including CVD health.[42] Cigarette smoking is one of the leading preventable causes of CVD (and other diseases) in the United States, and its prevention has been the focus of extensive public health efforts. In adults with T1D, smoking was associated with progression of CIMT in the DCCT-EDIC study[145] and arterial stiffness in the EDC study.[146] Use of tobacco was reported in 2.7% of 10- to 14-year-olds, 17.1% of 15- to 19-year-olds), and 34.0% of individuals older than 20 years in the SEARCH study and was associated with higher TG and physical inactivity.[147] Schwab and colleagues have reported that in adolescents with T1D, smoking contributes to CVD via worsening glucose control, dyslipidemia, and endothelial function.[148] The SEARCH study also reported that less than 50% of 10- to 14-year-old participants with diabetes reported being counseled by their health care provider to not smoke or to stop smoking.[147] Smoking increases CVD risk factors, including deterioration of glucose control, lipids, and endothelial function[148] in T1D, and increases the risk of nephropathy, retinopathy, and neuropathy.[149]

The role of nutrition in CVD is well established,[150–152] and MNT improves CVD risk factors in adults with T2D.[152,153] ADA guidelines for MNT recommend adequate calories be provided for growth and development in children and adolescents and that the combination of carbohydrates, protein, and fat be adjusted to meet glucose, blood pressure, and lipid goals.[42] Adults with T1D in the CACTI study reported higher than recommended intake of fat and saturated fat that was associated with worse glucose control, CVD risk factors, and CAC.[154] Most studies indicate that youth with diabetes fail to meet recommended nutritional intake of fruits, vegetables, and whole grains but exceed recommended intake of fat.[155–159] The SEARCH study reported that adherence to the DASH diet was associated with lower blood pressure, a better HDL/LDL ratio, and lower HbA1c level in youth with T1D.[161] Of interest, both sugar-sweetened beverage and diet beverage intake were also associated with a higher HbA1c level, higher blood pressure, and higher lipids.[162] Healthy diet has an important—and complex—role in T1D management both for glucose control and for CVD risk reduction. For example, the standard of care for meal-time insulin dosage is based on concurrent blood glucose and carbohydrate intake; however, protein and fat intake (as well as dietary fiber) can influence blood glucose levels,[163,164] with potential effects on dietary choices and CVD risk.

Physical activity is recommended as an integral part of T1D management.[42] Adults with diabetes are advised to exercise for more than 150 min/wk, and it is recommended by the AAP that youth engage in 60 minutes of moderate-to-vigorous physical activity daily. Several studies suggest that youth with T1D are more sedentary and less fit than nondiabetic youth.[165–167] One study in adults reported no difference in physical activity between adults with and without T1D and that physical inactivity and smoking were both associated with CAC.[168] The EDC study found a beneficial association between physical activity and CVD and mortality.[169]

Nonmodifiable Risk Factors

Nonmodifiable CVD risk factors in T1D include genetics, family history, and diabetes duration. There have been numerous investigations into genetic risk factors for CVD in general[170] and in T1D specifically (see also Chapter 3).[171,172] Systems under investigation for potential increased genetic risk for CVD in T1D were reviewed by Orchard and colleagues[41] and include polymorphisms in the receptors for advanced glycation end products, ACE, neuropeptide Y, hepatic lipase, apolipoprotein A-IV, von Willebrand factor, haptoglobin, nitric oxide synthase, and adiponectin.[41,173] In addition to genetics, a family history of T2D increased CVD[174] and in the DCCT-EDIC trials was associated with increased weight gain and a more atherogenic CVD profile among those in the intensive arm with a more atherogenic CVD profile.[75] Duration of T1D is consistently and not unexpectedly a risk factor for complications in general and for CVD specifically. For example, a 20- or 30-year duration of T1D confers an increased risk for CVD as compared with a similarly aged and controlled patient who was recently diagnosed. In addition, unlike in the general population, female patients with T1D lack the benefit of reduced CVD risk as compared with male patients.[37,175–177]

SUMMARY

The pathophysiology of CVD in T1D is complex, with many risk factors contributing to its increased rate and earlier onset. Poor glucose control as a result of underinsulinization or, in contrast, hyperinsulinization in intensive control (with obesity as a potential contributor) can each contribute to CVD. However, intensive diabetes control to achieve near euglycemia with a healthy diet, physical activity, a healthy weight, and abstinence from tobacco is the basis of CVD health in patients with T1D. Pharmacologic treatment of CVD risk factors and the thresholds for initiation and goals of treatment are evolving as data accumulate on safety, efficacy, and health outcomes. Currently, limited data exist from clinical trials on the relative risks for each CVD risk factor on CVD outcomes or on how interventions improve CVD outcomes in T1D. With advances in therapy for glucose control in T1D such as the artificial pancreas on the horizon, the characteristics of CVD in T1D are likely to evolve. CVD health will continue to be an important aspect of health care in patients with T1D.

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PART III

Management of Coronary Heart Disease Risk and Disease in Patients with Diabetes

12 Effect of Lifestyle Interventions on Coronary Heart Disease Risk in Patients with Diabetes

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In the United States, the prevalence of high cholesterol, hypertension, and cigarette smoking together with age-adjusted cardiovascular deaths has declined over the last several decades.[1] On the other hand, the prevalence of diabetes has risen steadily, largely because of an epidemic of obesity and adiposity and our increasingly inactive lifestyle (see also Chapters 1 and 5).[2] These trends will likely mitigate further reductions in cardiovascular mortality and even reverse the decline in cardiovascular disease (CVD) incidence.[3]

Using 2010 as the baseline, the estimated direct and indirect costs of CVD are expected to triple by the year 2030, making this a critical medical and societal issue.[4,5] These sobering projections and other recent data[6,7] suggest that effective preventive strategies are needed if we are to limit the growing burden of CVD (see also Chapters 5 and 6). The current reactive-based health care model, in which patients are seen when they become ill, typically during outpatient visits or hospitalizations, often fails to proactively improve health, because so many health outcomes are explained by individual behaviors and the lifestyle choices people make on a daily basis.[6,8]

Unfortunately, many patients as well as individuals in the medical community continue to rely on costly coronary revascularization procedures and/or cardioprotective medications as a first-line strategy to stabilize or favorably modify established risk factors and the course of coronary heart disease (CHD). However, these therapies do not address the root of the problem, that is, the most proximal risk factors for CHD, including poor dietary practices, physical inactivity, and cigarette smoking, as shown in **Figure 12-1**.[3] Unhealthy lifestyle habits strongly influence not only conventional risk factors (e.g., blood pressure, lipid and lipoprotein levels, glucose-insulin homeostasis) but also novel or emerging risk factors such as endothelial function, inflammation (e.g., C-reactive protein), thrombosis and coagulation, arrhythmias, and other disease modulators (e.g., psychosocial stressors),[3] even among users of lipid-lowering and antihypertensive medications.[9] Collectively, these data suggest it is time to change our emphasis from disease management to disease prevention, focusing on the foundational causes of CVD by reengineering prevention into the U.S. health care system.[7]

This chapter emphasizes the role of lifestyle interventions in the prevention and treatment of CVD in patients with diabetes, with specific reference to weight management and energy balance, dietary intake and cardiometabolic risk, smoking cessation, exercise and physical activity, cardiorespiratory fitness, and research-based psychosocial

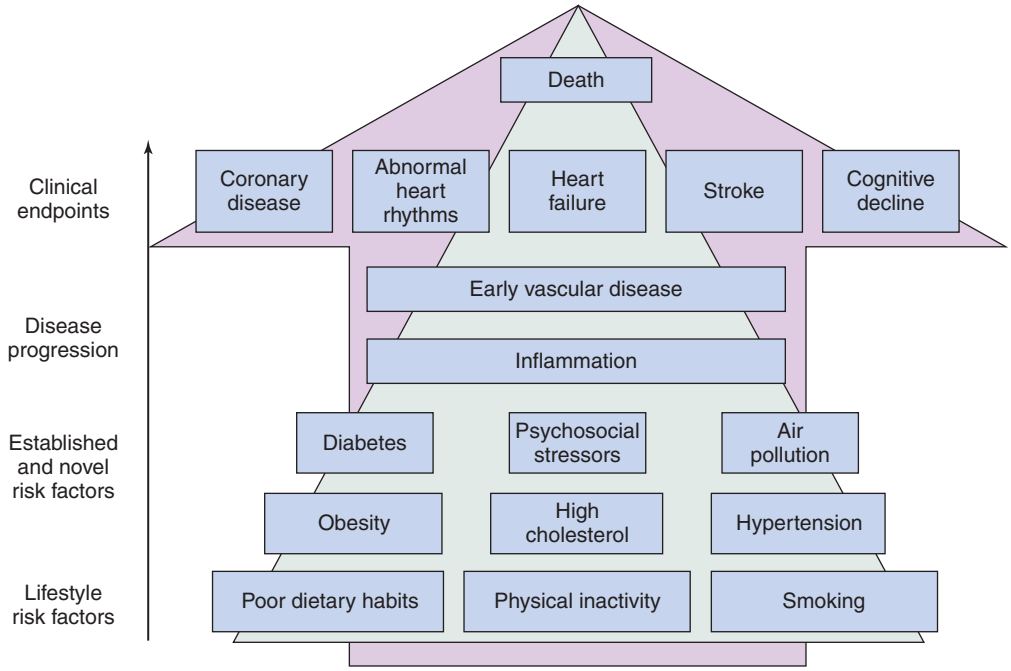


FIGURE 12-1 Unhealthy lifestyle habits lead to coronary risk factors, the progression of cardiovascular disease, and ultimately adverse outcomes or clinical endpoints. Thus the first-line strategy to prevent coronary heart disease (or recurrent cardiac events) is to favorably modify poor lifestyle habits or practices, including suboptimal dietary habits, physical inactivity, and cigarette smoking. *(Modified from Mozaffarian D and colleagues.[3])*

interventions (e.g., readiness for changes, motivational interviewing, counseling strategies) to support cardioprotective lifestyle change in this at-risk patient subset (see also Chapter 5).

WEIGHT MANAGEMENT AND ENERGY BALANCE

Obesity is an independent risk factor for hypertension, dyslipidemia, and CVD, increasing the risk of cardiovascular events and mortality in patients with type 2 diabetes.[10–12] Distribution of body fat also plays a role in cardiometabolic risk; individuals with central adiposity, as evidenced by increased waist measurement or "apple" body shape, have higher risk.[13] Elevated waist circumference is defined as greater than 100 cm (40 inches) for North American men and greater than 88 cm (35 inches) for North American women.[14] The proposed Diabetes Federation cut points for other geographical areas and countries are somewhat lower.[15] Most individuals with type 2 diabetes are overweight or obese and/or have an elevated waist circumference. Therefore weight reduction is commonly indicated for patients with type 2 diabetes.

Increased waist measurement is a surrogate marker for visceral adiposity, which is fat tissue within the peritoneal cavity surrounding the intra-abdominal organs. Visceral adiposity is metabolically active, secreting a number of cytokine-like factors, referred to as *adipokines*. Adipokines promote inflammation and a prothrombotic state and are associated with development of atherogenic dyslipidemia (hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol [HDL-C] level, and an elevated subfraction of small, dense low-density lipoprotein [LDL] cholesterol [LDL-C] level), insulin resistance, dysglycemia and elevated blood pressure.[16] Inflammation, as measured by serum level of high-sensitivity C-reactive protein, is also associated with type 2 diabetes and CVD.[17] Modest weight reduction of 5% total body weight in individuals with type 2 diabetes is associated with decreased visceral adiposity and improvement in serum lipid concentrations, insulin action, and fasting blood glucose, as well as reductions in blood pressure, serum markers of inflammation, and the need for diabetes medication(s).[18] In some patients, substantial weight loss can lead to clinical resolution of type 2 diabetes (see also Chapters 2, 9, and 10).[19]

Weight loss occurs when energy intake is lower than energy expenditure. An energy deficit of 500 to 1000 kcal/day (3500 to 7000 kcal/wk) usually results in a weight loss of 1 to 2 lb/wk. Rate of weight loss can vary, however, depending on genetic factors, age, fidgeting, amount of lean body mass, and habitual physical activity. Older individuals tend to lose weight more slowly than younger persons because metabolic rate declines by approximately 2% each decade.[20] A higher lean body mass is associated with greater energy expenditure and therefore a higher rate of weight loss. Most overweight or obese adults will lose weight if they comply with a diet of 1000 to 1200 kcal/day for women or 1200 to 1600 kcal/day for men.[14] An alternative approach to determining prescribed calorie content is based on current total body weight and is divided into five weight categories (**Table 12-1**).[21]

Investigators have attempted to define the dietary macronutrient composition that is optimal for weight reduction, improvement in cardiometabolic risk factors, and long-term weight maintenance in overweight and obese individuals, as well as patients with type 2 diabetes (see also Chapter 5). Overall, it appears that lower-carbohydrate diets (<40% of total calories) may result in greater short-term weight loss, improvement in hypertriglyceridemia, and possibly improvement in insulin resistance and glycosylated hemoglobin, but degree of weight loss and improvement in cardiometabolic

TABLE 12-1 Determining Prescribed Calorie Content

PRESCRIBED CALORIE CONTENT (KCAL/DAY)	CURRENT TOTAL BODY WEIGHT (POUNDS)
1000–1200	150–199
1200–1500	200–249
1500–1800	250–299
1800–2000	300–349
2000	300 or higher

risk factors is similar to that seen with low-fat or high-protein diets at 1 to 2 years.[22] Of note, however, is that many participants have difficulty maintaining the macronutrient composition of their assigned diet after 6 to 12 months, so the true impact of differing macronutrient composition dietary intake in the long term is not known. It is likely that the optimal macronutrient composition varies for different individuals with regard to long-term compliance. Therefore, dietary guidance should be individualized to the patient's lifestyle, preferences, and culture. According to the American Diabetes Association (ADA) 2013 Position Statement,[23] the mix of carbohydrate, protein, and fat may be adjusted to meet the metabolic goals and individual preferences of the person with diabetes.

The ADA, the Obesity Society, and the American Society for Nutrition recommend a 500- to 1000-kcal/day deficit through a diet that meets guidelines for reducing risk of comorbidities with obesity.[18] Specifically, these organizations recommend that the dietary macronutrient content and nutritional quality be based on guidelines from the ADA,[24] the American Heart Association (AHA),[25] and the National Cholesterol Education Program—Adult Treatment Panel (**Box 12-1**).[26] These are evidence-based dietary interventions that have been shown to improve selected cardiovascular risk factors, including hypertension and LDL-cholesterol level, and therefore are appropriate for patients with type 2 diabetes. According to the 2013 ADA Position Statement,[23] individuals who have prediabetes or diabetes should receive individualized medical nutritional therapy (MNT) as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT. The ADA statement recognizes that for weight loss, low-carbohydrate, low-fat, calorie-restricted, or Mediterranean diets may be effective in the short term (up to 2 years). However, for patients on low-carbohydrate diets, it is recommended to monitor lipid profiles, renal function, and protein intake (for those with nephropathy) and adjust hypoglycemic pharmacotherapy as needed.

Prepackaged meal replacements in the form of liquid shakes, bars, and entrees are a useful tool to simplify a prescribed diet and minimize errors with portion control and high-caloric-density food choices. Meal replacement diets can enhance weight loss, improve cardiovascular risk factors, and have shown durable weight loss for periods of 4 to 5 years.[27–32] A meal replacement weight loss diet typically consists of replacing two food meals and two snacks with four approximately 110- to 200-kcal shakes or bars, plus one food meal consisting of lean protein, low-starch vegetables, a fruit serving, and a starch serving. Total daily caloric intake often ranges from 900 to 1300 kcal/day. For weight maintenance, individuals typically have two food meals and replace a third meal and one to two snacks per day with a shakes and/or bars. In a study of 119 patients with type 2 diabetes, use of prepackaged meal replacements, compared with calorie-equivalent usual-care diet, resulted in greater weight loss (-3.0 ± 5.4 kg versus -1.0 ± 3.8 kg), improved glycemic control with lower hemoglobin A1c (HbA1c) levels, improved quality of life, and better compliance with dietary recommendations after 1 year.[27] Another study found that the use of liquid meal replacements for 12 weeks in patients with type 2 diabetes resulted in significantly greater weight losses and reductions in fasting blood sugar compared with a conventional diet with the same calorie goal.[33]

With the prescription of a meal replacement diet, care must be taken to lower or discontinue medications that can lead to significant hypoglycemia, such as sulfonylureas, insulin secretagogues, and insulin. Required medication adjustments are based on the patient's current glycemic control, the prescribed dietary carbohydrate content, and the anticipated rate of weight loss based on calorie deficit. Patients should monitor blood glucose on a scheduled basis, and assessment for further medication adjustments should be completed daily to weekly for the first 3 to 4 weeks on the diet and then at intervals of 2 to 4 weeks during weight loss.

Recently, the Look AHEAD (Action for Health in Diabetes) study[34] examined whether cardiovascular morbidity and mortality in persons with type 2 diabetes were reduced through an intensive lifestyle intervention aimed at achieving and maintaining at least a 10% loss of body weight over 4 years. This large randomized controlled trial of 5145 participants included moderate-intensity exercise with a goal of 200 min/wk, a healthy diet that included portion-controlled foods, and behavior modification, versus a usual-care control group (diabetes support and education). The primary outcome was a composite of death from cardiovascular causes, or hospitalization for angina pectoris for up to 13.5 years. One-year results showed an average 8.6% weight loss, significant reduction of glycosylated hemoglobin, and reduction in several cardiovascular risk factors in the intervention group. Other important health benefits included improvement in obstructive sleep apnea, reduction in diabetes medications, maintenance of physical mobility, and improvement in quality of life. However, despite these numerous health improvements, the intensive lifestyle intervention did not reduce the rate of cardiovascular events and the trial was halted early.

BOX 12-1 Dietary Guidelines Associated with Cardiovascular Risk Reduction

Eat a variety of fruits, vegetables, whole grains, legumes, and low-fat or nonfat dairy products.
- Choose lean meats and poultry without skin, and prepare them without added saturated and trans fat.
- Consume two or more servings of fish per week (with the exception of commercially fried fish fillets).
- Limit saturated fat to less than 7% of total calories.
- Minimize intake of *trans* fat by greatly limiting foods containing partially hydrogenated vegetable oil.
- Limit dietary cholesterol intake to less than 200 mg/day.
- Consume 20 to 30 g of fiber daily.
- Greatly limit foods and beverages with added sugars.
- Choose and prepare foods with little or no salt. Limit sodium intake to 2300 mg/day or less, according to ADA guidelines (or less than 1500 mg/day per AHA guidelines).
- Limit alcohol intake to ≤ two drinks per day for men and ≤ one drink per day for women.

Data from the ADA,[24] the AHA,[25] and the National Cholesterol Education Program Expert Panel.[26]

Dietary Intake and Cardiometabolic Risk

The ADA MNT goals include achieving and maintaining blood glucose levels in the normal range or as close to normal as safely possible, a lipid and lipoprotein profile that reduces the risk for CVD, and blood pressure levels in the normal range or as close to normal as possible.[24] In type 2 diabetes, there is evidence that more intensive treatment of glycemia, particularly in newly diagnosed diabetes, may reduce long-term CVD events. The glycosylated hemoglobin goal according to ADA guidelines is below 7.0% but should be individualized based on factors such as age and life expectancy, comorbid conditions, and hypoglycemia unawareness. MNT has been shown to reduce glycosylated hemoglobin levels by 1% to 2% in type 2 diabetes, depending on duration of diabetes.[35,36] Lowering of LDL-C to a target of less than 100 mg/dL has been shown to decrease cardiovascular risk in type 2 diabetes; and for high-risk individuals with overt CVD, an LDL-C goal of below 70 mg/dL is recommended.[37] There is also evidence that lowering blood pressure to below 140 mm Hg systolic and below 80 mm Hg diastolic in individuals with type 2 diabetes reduces cardiovascular events.[38,39] Accordingly, the ADA guidelines recommend a systolic blood pressure target of below 140 mm Hg and a diastolic blood pressure target of below 80 mm Hg.

Dietary carbohydrate intake is the major determinant of postprandial blood glucose levels, which in turn have a significant impact on overall diabetes control and glycosylated hemoglobin level. Therefore the impact of carbohydrate intake on blood sugars with regard to carbohydrate amount, type, glycemic index, and glycemic load has been the focus of several investigations. Glycemic index is a measure that compares postprandial blood glucose responses to constant amounts of different carbohydrate-containing foods.[40] Glycemic load is calculated by multiplying the glycemic index of the food by the amount of carbohydrate. Fiber, lactose, fructose, and fat tend to lower glycemic index. Examples of carbohydrate foods with a lower glycemic index include oats, barley, bulgur, lentils, apples, oranges, milk, and yogurt. High–glycemic index foods include items such as white bread, most white rice, potato, pretzels, corn flakes, and extruded breakfast cereals. A meta-analysis of the effects of low–glycemic index diets on blood sugar control found a 0.4% reduction in glycosylated hemoglobin in comparison with high–glycemic index diets.[41] In addition to the modest benefit of low–glycemic index diets on glycosylated hemoglobin, many low–glycemic index foods have higher nutritional quality with regard to fiber, vitamins, and minerals. The ADA recommends a diet that includes carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat milk, which are lower–glycemic index foods.

The total amount of carbohydrate in a meal also affects postprandial glucose levels. The recommended daily allowance for carbohydrate intake is 130 g/day, which is the average minimum requirement.[42] There are no large randomized long-term trials that evaluate outcomes of low-carbohydrate diets specifically in individuals with diabetes. One small weight loss trial reported improvement in fasting glucose among a subset with diabetes after 1 year on a lower-carbohydrate diet (120 g/day) compared with a higher-carbohydrate diet (230 g/day), but no significant change in glycosylated hemoglobin.[43] Because of lack of long-term data on the safety of low-carbohydrate diets in patients with diabetes as well as minimal evidence of benefit, it is recommended that clinicians focus on the nutritional quality of carbohydrates rather than the quantity of carbohydrates. Therefore, counseling diabetic patients to consume most or all of their carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat milk is preferred.

Dietary strategies associated with reducing blood pressure in individuals with diabetes include the DASH (Dietary Approaches to Stop Hypertension) diet and moderation of alcohol intake. The DASH diet is high in fruit and vegetables, moderate in low-fat dairy products, and low in animal protein and includes a substantial intake of plant protein from legumes and nuts. This diet, which is promoted by the National Heart, Lung and Blood Institute for the prevention and treatment of hypertension, substantially reduces both systolic and diastolic blood pressure.[44] Additional sodium restriction in combination with DASH results in even greater blood pressure lowering.[45] The ADA recommends a reduced-sodium diet (e.g., 2300 mg/day) for normotensive and hypertensive individuals with diabetes. The DASH diet has also been shown to reduce LDL-C.[46] A large prospective cohort study from the Nurses' Health Study found that adherence to the DASH-style diet was associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up.[47]

Chronic excessive alcohol intake is associated with increased risk of hypertension, whereas light-to-moderate alcohol intake is associated with reductions in blood pressure.[38] Therefore it is recommended that adults with diabetes who choose to drink alcohol should limit consumption to a moderate amount, defined as 1 drink or less per day for women and 2 drinks or less per day for men, ideally with meals.

Findings from large trials on dietary fat intake and cardiovascular outcomes in individuals with diabetes are not available. Because patients with diabetes have similar cardiovascular risk as those with preexisting CVD, the same dietary goals are recommended. These include limiting saturated fat intake to less than 7% of total calories, minimizing *trans* fatty acids, and limiting cholesterol intake to less than 200 mg daily. Saturated and *trans* fatty acids are the main dietary determinants of LDL-C, and reduction of dietary intake of these fats has been shown to decrease plasma total cholesterol and LDL-C. Dietary n-3 polyunsaturated fatty acids appear to have beneficial effects on plasma lipid concentrations, lowering plasma triglycerides in individuals with hypertriglyceridemia and type 2 diabetes. Both fish and fish oil supplements contain n-3 polyunsaturated fatty acids, and consumption from either source may reduce adverse CVD outcomes.[48] Other recent analyses, however, have reported no additional cardioprotective benefit from omega-3 fatty acid supplementation.[49,50] The ADA guidelines recommend two or more servings of fish per week (with the exception of commercially fried fish filets).

Smoking Cessation

Smoking is an independent risk factor for all-cause mortality in patients with diabetes, mainly because of CVD.[51] There is also a higher risk of stroke in diabetic patients who smoke compared with those who do not smoke.[52] The Nurses' Health Study found there is a higher relative risk of CVD among women who smoke a higher number of cigarettes per day as well as an increased relative risk based on pack-years.[53] However, this study also found that quitting smoking for 10 or more years virtually eliminated excess mortality risk.



Smoking is associated with cardiovascular risk factors including elevated serum total cholesterol and LDL-C levels, low serum HDL-C levels, and insulin resistance.[54] In addition, smoking is associated with poorer glycemic control.[55,56] In patients with type 1 diabetes, smokers have higher levels of intracellular adhesion molecule-1, which is a marker of endothelial dysfunction, compared with nonsmokers.[57]

Given the greatly increased cardiovascular risk associated with smoking in those with diabetes as well as the near elimination of increased risk 10 years after quitting, smoking cessation is an important lifestyle change target for cardiovascular risk reduction in individuals with diabetes. The ADA recommends including smoking cessation counseling and other forms of treatment as routine components of diabetes care.[24] A number of large randomized controlled trials demonstrate that even brief counseling on smoking cessation, including the use of quit dates, can be efficacious and cost-effective. For the patient who is motivated to quit, pharmacologic therapy in addition to counseling is more effective than either treatment alone.[58] There is also evidence that smoking cessation programs are cost-effective and successful in patients with diabetes. One proposed strategy for clinicians managing smoking in diabetic patients is the five *A*s strategy[59]:

1. Ask every patient about tobacco use.
2. Advise the patient about the importance of smoking cessation at every visit, in a brief, clear, and unambiguous manner.
3. Assess the patient's willingness to quit smoking within the next 30 days.
4. Assist the patient who is interested in quitting by offering self-help material, setting a quit date, offering referral to a local support group, and considering nicotine replacement therapy.
5. Arrange follow-up with those patients who are ready to quit, and give positive reinforcement during the first year after cessation.

EXERCISE AND PHYSICAL ACTIVITY IN THE PREVENTION AND TREATMENT OF TYPE 2 DIABETES MELLITUS

There is a pathophysiologic cascade by which physical inactivity predisposes to a cluster of cardiometabolic diseases, including type 2 diabetes mellitus. With an increasingly inactive lifestyle, skeletal muscle downregulates its capacity to convert nutritional substrates to adenosine triphosphate. Inactive skeletal muscle's impaired ability to oxidize glucose and fatty acids is presumably mediated by several mechanisms, including decreased mitochondrial concentration and oxidative enzymes; a reduced ability to remove glucose from blood because of fewer capillaries and diminished glucose transporter; and an attenuated capacity to hydrolyze blood triglycerides to free fatty acids, secondary to decreased lipoprotein lipase activity.[60] Collectively, these metabolic perturbations reduce the somatic capacity to burn fuel, resulting in hyperinsulinemia, insulin resistance, and hypertriglyceridemia, and ultimately increased cardiovascular risk. On the other hand, regular moderate-to-vigorous leisure-time physical activity, structured aerobic exercise, or both, can often reverse these adverse sequelae. A significant increase in physical activity and daily energy expenditure also improves insulin action in obesity, with or without a concomitant reduction in body weight and fat stores.[61] This is an important (and often overlooked) salutary effect, suggesting that physical activity is as efficacious in preventing insulin resistance as losing body weight.

Several recent randomized controlled trials in patients with type 2 diabetes have investigated the effects of moderate-to-vigorous aerobic exercise and resistance training on cardiorespiratory fitness, modifiable cardiovascular risk factors, and arterial stiffness, with specific reference to changes in body weight and fat stores.[62–64] Compared with the control group and/or counseling alone, supervised exercise produced significant improvements in cardiorespiratory fitness, upper and lower body strength, HbA1c, systolic and diastolic blood pressure, total serum cholesterol, HDL-C and LDL-C, body mass index (BMI), waist circumference, insulin resistance, inflammation (high-sensitivity C-reactive protein), leptin, and CHD risk scores, independent of body weight losses. Structured exercise durations exceeding 150 min/wk were associated with greater HbA1c declines than those of 150 min/wk or less (0.89% and 0.36% reductions, respectively).[65] On the other hand, large-artery elasticity, assessed by measuring pulse wave velocity, did not improve.[62] A systematic review and meta-analysis of the relevant literature from 1970 to 2009 revealed that combined aerobic exercise and resistance training, as well as aerobic exercise alone, were related to statistically significant declines in HbA1c, triglyceride levels, waist circumference, and systolic blood pressure among individuals with type 2 diabetes.[66] In contrast, the meta-analysis found little support for the benefits of resistance training alone on cardiovascular risk factors, including changes in HbA1c or resting systolic blood pressure, in patients with diabetes. Others, however, have reported that resistance training alone is associated with reductions in HbA1c as compared with a control group of patients with type 2 diabetes.[65]

Compared with overweight and obese individuals, those with a normal weight at the time of diabetes diagnosis have higher mortality rates, even after adjustment for potential confounding variables.[67] Because these data extend the "obesity paradox" to patients with diabetes, other potential modulators of survival, including body composition, fat distribution, regular physical activity, and cardiorespiratory fitness, beyond the measurement of BMI, may help the medical community clarify the relationships among obesity, morbidity, and mortality in adults with diabetes.[68]

Numerous investigations and systematic reviews have examined the relationships among habitual physical activity, cardiorespiratory fitness, diabetes, BMI, and mortality. The risk for all-cause and/or cardiovascular mortality is lower among overweight and obese individuals with good aerobic fitness than in individuals with normal BMI and low fitness.[69,70] This finding has also been reported in a study of African American and Caucasian veterans with diabetes, in whom the obesity paradox was observed along with an independent association between poor exercise capacity and mortality within BMI categories.[71] Others have reported that higher levels of cardiorespiratory fitness are associated with a substantial reduction in health risk for a given level of visceral and subcutaneous fat,[72] and that increased physical activity and/or cardiorespiratory fitness is inversely associated with all-cause and cardiovascular mortality in persons with diabetes.[68,73–75] Collectively, these data and other recent reports[76,77] strongly support the role of structured exercise, regular moderate-to-vigorous physical activity, or both, in interventions designed to prevent and treat type 2 diabetes, regardless of the patient's BMI.

Walking: "Exercise is Medicine" for Patients with Diabetes

Epidemiologic studies and clinical trials have consistently demonstrated the survival benefits of regular exercise, especially walking, in the prevention and treatment of type 2 diabetes mellitus (see also Chapter 5). In epidemiologic studies, brisk walking for at least 30 min/day has been associated with a 30% to 40% reduction in the risk of developing type 2 diabetes in women.[78] Two clinical trials demonstrated that regular walking or other moderate exercise in conjunction with dietary changes and modest weight losses resulted in a 58% reduction in the development of diabetes in overweight patients with impaired fasting glucose, as compared with usual-care control groups.[79,80] In the Diabetes Prevention Program, drug therapy with metformin reduced the risk by only 31%.

In a nationally representative sample (n = 2896) of Americans with diabetes aged 18 years or older, regular walking was associated with significant reductions in all-cause and cardiovascular mortality, up to 39% and 54% for walking at least 2 hr/wk and 3 to 4 hr/wk, respectively.[81] The inverse association held in multivariable analyses after potential confounding variables (e.g., risk factors, BMI, comorbid conditions) were controlled for. Walking at moderate-intensity levels was associated with the greatest reduction in mortality rates. The authors concluded that "1 death per year may be preventable for every 61 people who could be persuaded to walk at least 2 hours [per] week." These findings are consistent with previous studies conducted among younger and healthier populations with diabetes. In the Nurses' Health Study, in which baseline CVD and cancer patients were eliminated, moderate and vigorous levels of physical activity were associated with reduced rates of overall cardiovascular events among diabetic women aged 30 to 55 years.[82] Similarly, the Aerobics Center Longitudinal Study reported that men with type 2 diabetes who had a low fitness level and were physically inactive had higher mortality rates during follow-up than did their counterparts who were active and fit.[73] The clinical and public health implications of these data are enormous, because the survival benefits of moderate- to vigorous-intensity exercise, often achieved by brisk walking alone, may be even greater than those achieved by contemporary pharmacologic therapies to manage diabetes.[83]

Cardioprotective Effects of Regular Exercise

Two meta-analyses[84,85] have now shown that regular exercise participation can decrease the overall risk of cardiovascular events by up to 50%, presumably from multiple mechanisms, including antiatherosclerotic, anti-ischemic, antiarrhythmic, antithrombotic, and psychological effects (**Fig. 12-2**). As noted earlier, aerobic exercise, with and without resistance training, has favorable effects on the diabetic patient's cardiovascular risk factor profile, as well as on coagulability, fibrinolysis, and coronary endothelial function. Because more than 40% of the risk reduction associated with exercise training cannot be explained by changes in conventional risk factors, a cardioprotective "vascular conditioning" effect, including enhanced nitric oxide vasodilator function, improved vascular reactivity, altered vascular structure, or combinations thereof, has been proposed.[86] Decreased vulnerability to threatening arrhythmias and increased resistance to ventricular fibrillation have also been postulated to reflect exercise-related adaptations in autonomic control. As a result of endurance training, sympathetic drive at rest is reduced and vagal tone and heart rate variability are increased. Moreover, ischemic preconditioning before coronary occlusion, at least in animal models, can reduce subsequent infarct size and/or the potential for malignant ventricular arrhythmias.[87,88]

PHYSICAL ACTIVITY, EXERCISE PROGRAMMING, AND PRESCRIPTION

In many patients with type 2 diabetes, adequate glycemic control can often be achieved by dietary changes, regular physical activity, structured exercise, and weight reduction. The exercise program should generally follow contemporary guidelines for the treatment of excessive body weight and fat stores,[89] and other risk factors associated with this common metabolic condition (i.e., dyslipidemia, hypertension, inflammatory markers, fibrinolytic factors, waist circumference). Overall, individuals with type 2 diabetes have an increased risk of morbidity and mortality from CVD as compared with their age- and gender-matched counterparts without this comorbidity. Accordingly, a physical examination and a careful preliminary cardiovascular assessment, including peak or symptom-limited exercise testing, with estimated or directly measured peak oxygen consumption ($\dot{V}O_2$ peak), should be considered before beginning a vigorous ($\geq$60% $\dot{V}O_2$ reserve) exercise training program, where

$$\dot{V}O_2 \text{ reserve} = \% \text{ intensity} \times (\dot{V}O_2 \text{ peak} - \dot{V}O_2 \text{ rest}) + \dot{V}O_2 \text{ rest}$$

With this formula, $\dot{V}O_2$ is generally expressed in mL O_2/kg/min or in metabolic equivalents (METs), where 1 MET = 3.5 mL O_2/kg/min. Both the AHA[90] and the American College of Sports Medicine (ACSM) guidelines for exercise testing and prescription[91] recommend that peak or symptom-limited exercise testing be considered before initiation of vigorous exercise training in individuals with known or suspected CVD, including patients with diabetes mellitus.[92]

Type of Exercise

Aerobic (or endurance) exercise has been the most frequently studied mode of physical conditioning, and the resultant increases in cardiorespiratory fitness in patients with type 2 diabetes have been consistently associated with improvements in modifiable cardiovascular risk factors, independent of weight loss.[64] The most effective exercises for the endurance phase use large muscle groups, are maintained continuously, and are rhythmic in nature, such as walking, jogging, elliptical training, stationary or outdoor cycling, swimming, rowing, stair climbing, and combined arm-leg ergometry. Other exercise modalities commonly used in structured exercise training programs for patients with type 2 diabetes include calisthenics, particularly those involving sustained total-body movement, recreational activities (e.g., golf, doubles tennis, pickleball), and resistance training.[93] The last is a particularly important option, because traditional aerobic-conditioning regimens often fail to accommodate participants who require improved muscle strength or endurance to perform occupational or leisure-time activities. Moreover, studies have now shown that muscular strength is inversely associated with all-cause mortality, independent of cardiorespiratory fitness levels.[94]

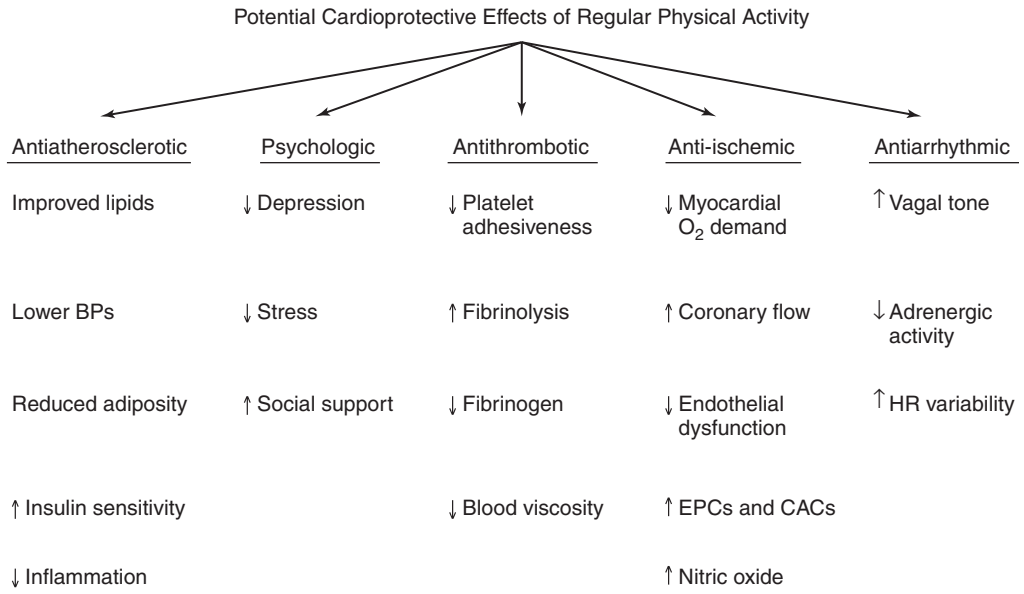


FIGURE 12-2 A structured endurance exercise program, increased lifestyle physical activity, or both, sufficient to maintain and enhance cardiorespiratory fitness may provide multiple mechanisms to reduce nonfatal and fatal cardiovascular events in "at-risk" patients with diabetes. BP = Blood pressure; CACs = cultured angiogenic cells; EPCs = endothelial progenitor cells; HR = heart rate; O_2 = oxygen; ↑ = increased; ↓ = decreased.

Because of the high prevalence of underlying ischemic heart disease, and the heightened risk for exertion-related cardiovascular events and orthopedic injuries, adoption of a moderate intensity (e.g., walking), rather than a vigorous physical activity program (e.g., jogging, running) may be more appropriate for diabetic patients, especially those who are middle-aged and older.[83] Walking has several advantages over other forms of exercise during the initial phase of a physical conditioning program, including inherent neuromuscular limitations on the speed of walking (and therefore the rate of energy expenditure). Brisk walking programs can significantly increase aerobic capacity and reduce body weight and fat stores, particularly when the walking duration exceeds 30 minutes.[95] Additional advantages of a walking program include accessibility, social companionship, lack of special equipment (other than a pair of well-fitted athletic shoes), an easily tolerable exercise intensity, and fewer musculoskeletal and orthopedic problems of the legs, knees, and feet than with jogging or running. Walking in water,[96] with a backpack, or with a weighted vest[97] are options for those who seek to progressively increase the exercise intensity and associated energy expenditure.

The Rule of 2 and 3 Miles per Hour (mph)

Because most diabetic patients, many of whom are overweight or obese, prefer to walk at moderate intensities, it is helpful to recognize that walking on level ground at 2 and 3 mph approximates 2 and 3 METs, respectively. For patients who prefer the slower walking pace (2 mph; 3.2 km/h), each 3.5% increase in treadmill grade adds approximately 1 MET to the gross energy cost. Therefore, patients who desire to walk at a 2-mph pace, but require a 4-MET workload for training, would be advised to add 7.0% grade to this speed. For patients who can negotiate the faster walking speed (3 mph; 4.8 km/h), each 2.5% increase in treadmill grade adds an additional 1 MET to the gross energy expenditure. Accordingly, a workload of 3 mph, 7.5% grade, would approximate an aerobic requirement of 6 METs. Use of this practical rule can be helpful to clinicians in prescribing treadmill exercise workloads for their diabetic patients, without the need for consulting tables, nomograms, or metabolic formulas or calculations.[98]

Resistance Training

Although resistance exercise has generally been considered to be less effective in preventing and treating type 2 diabetes, some reviews suggest that it provides independent and additive benefits to an aerobic exercise program for virtually the entire cluster of associated cardiovascular risk factors.[99] For example, numerous studies show that resistance training improves insulin sensitivity, significantly decreases HbA1c and blood pressure in diabetic and hypertensive adults, respectively, and reduces body fat stores and visceral adipose tissue in both men and women. In addition, the maintenance or enhancement of lean body mass from chronic resistance training is associated with a modest increase in basal metabolic rate, which over time may facilitate greater reductions in body weight than can be achieved with increased physical activity and/or structured exercise. Weight-training–induced attenuation of the hemodynamic response to lifting standardized loads has also been reported, which may decrease cardiac demands during daily activities such as carrying packages or lifting moderate to heavy objects.[100] There are also intriguing data to suggest that strength training can increase endurance capacity without an accompanying increase in cardiorespiratory fitness.[101]

Although the traditional weight-training prescription has involved performing each exercise three times (e.g., three sets of 10 to 15 repetitions per set), it appears that one set provides similar improvements in muscular strength and endurance, at least for the novice exerciser.[102] Consequently, single-set programs performed at least two times a week are recommended rather than multiset programs, because they are highly effective, less time-consuming, and less likely to cause musculoskeletal injury or soreness. Such regimens should include 8 to 10 different exercises involving the trunk and upper and lower extremities at loads that permit 8 to 15 repetitions per set. At least 60 minutes of resistance training should be completed each week (e.g., two 30-minute sessions).

Lifestyle Physical Activity

Despite contemporary exercise guidelines and the much-heralded Surgeon General's report,[103] the traditional model for getting people to be more physically active (i.e., a regimented or structured exercise program) has been only marginally effective. Randomized clinical trials have now shown that a lifestyle approach to physical activity among previously sedentary adults has similar effects on cardiorespiratory fitness, body composition, and coronary risk factors as a structured exercise program.[104,105] These findings have important implications for public health, suggesting an alternative approach to sedentary people who, for one reason or another, are not ready to integrate a formal exercise commitment into their daily schedule.[106] The skyrocketing prevalence of overweight and obesity and related sequelae (e.g., type 2 diabetes, metabolic syndrome) suggests the need for "real world" interventions designed to circumvent and attenuate barriers to achieving an adequate daily energy expenditure.[107] Accordingly, physicians and allied health professionals should counsel patients to integrate multiple short bouts of physical activity into their lives.[108] Nonexercise activity thermogenesis—the spontaneous physical activities of daily living (e.g., fidgeting while sitting, standing while reading, moving the lower extremities while working at the computer)—represents another source of energy expenditure for many people.[109] Standing also elevates lipoprotein lipase, an enzyme that improves fat metabolism while reducing insulin resistance.[110,111] Thus, energy expenditure during nonexercise time may be as critical for preventative health as structured exercise time. Pedometers can be helpful in this regard, as can programs that use them (e.g., America on the Move) to enhance awareness of physical activity by progressively increasing daily step totals. According to one systematic review, pedometer users significantly increased their physical activity by an average of 2491 steps per day more than their control counterparts.[112] The Activity Pyramid (**Fig. 12-3**) has also been suggested as a model to combat America's increasingly hypokinetic environment.[113] This schematic presents a tiered set of weekly goals to promote improved cardiorespiratory fitness and health, building on a base that emphasizes the importance of accumulating at least 30 minutes of moderate-intensity activity on 5 or more days per week.

Intensity and Duration

There is some controversy regarding the most appropriate exercise intensity and duration that are needed to optimally physically condition patients with insulin resistance syndrome.[114] Different risk factors associated with this condition may respond more favorably to different exercise dosages and intensities. For example, a randomized, controlled trial of previously inactive, overweight men and women with abnormal lipoprotein profiles compared the effectiveness of three different exercise regimens versus controls: high-amount, high-intensity exercise; low-amount, high-intensity exercise; and low-amount, moderate-intensity exercise.[115] Although all exercise groups demonstrated improved responses on a variety of lipid and lipoprotein variables as compared with the control group, the most beneficial changes were noted in the high-amount, high-intensity exercise regimen. Because type 2 diabetes has been associated with increased body weight and fat stores, a sedentary lifestyle, and a low level of cardiorespiratory fitness, the initial exercise intensity should approximate at least 40% of the $\dot{V}O_2$ or heart rate reserve or 55% of the maximal heart rate, at a rating of perceived exertion (6 to 20 category scale) of 11 (fairly light) or higher, for a minimum accumulated duration of 30 min/day.[116,117] Over time, in the absence of adverse signs and symptoms, the exercise intensity should be gradually increased, generally corresponding to a rating of perceived exertion up to 14 (somewhat hard to hard), to provide the stimulus to improve cardiorespiratory fitness

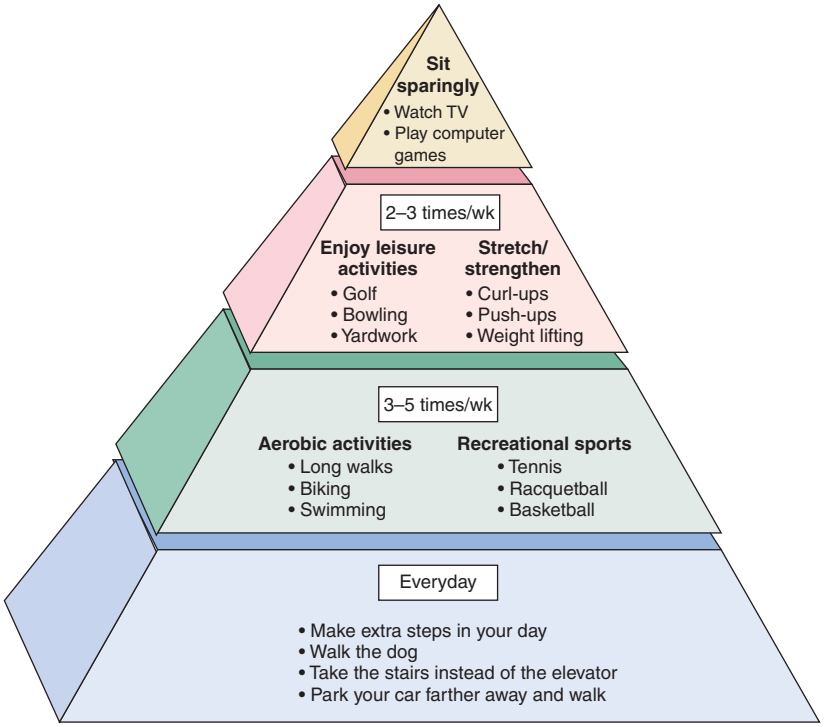


FIGURE 12-3 The Activity Pyramid, analogous to the U.S. Department of Agriculture (USDA) Food Guide Pyramid, has been suggested as a model to facilitate public and patient education for adoption of a progressively more active lifestyle. *(Copyright ©1996 Park Nicollet Health-source Institute for Research and Education. Reprinted with permission).*

and facilitate a progressive overload (i.e., attainment of goal energy expenditure).

The exercise intensity recommendation can be achieved with a combination of moderate and vigorous physical activity, which approximates 40% to 59% and 60% to 84% of $\dot{V}O_2$ or heart rate reserve, respectively. The ACSM recommends that most adults engage in moderate-intensity exercise training for at least 30 min/day on at least 5 days of the week for a total of more than 150 min/wk, or vigorous exercise training for at least 20 min/day on at least 3 days of the week for a total of more than 75 min/wk, or a combination of moderate and vigorous-intensity exercise to achieve a total energy expenditure of more than 500 to 1000 MET/min/wk.[118] When a combination is used, it has been suggested that the vigorous-intensity exercise time can be multiplied by 1.7 to allow this to be added to the moderate-intensity time.[116] For example, in 1 week a diabetic patient could exercise on 3 days for 40 minutes at a moderate intensity and on another day for 20 minutes at a vigorous intensity, approximating 154 minutes of moderate-intensity activity (120 + [20 × 1.7]). Thus, this combination of moderate and vigorous exercise meets the minimum recommended weekly moderate-intensity exercise dosage (≥150 minutes). The 1.7 multiplication factor is derived from recommendations that 150 minutes of moderate-intensity exercise is equivalent to approximately 90 minutes of vigorous physical activity (a ratio of 1:1.7), and is compatible with a recent position statement from the ACSM and ADA.[119]

Frequency

The frequency of exercise is an important consideration when structured exercise and/or increased lifestyle physical activity are used to treat the abnormalities associated with type 2 diabetes, especially insulin sensitivity and glucose use. Although even twice-weekly exercise sessions may favorably influence glycemic control, patients with type 2 diabetes should exercise at least 3 days each week with no more than 2 consecutive days without training,[117] because increases in insulin sensitivity decline markedly by 48 hours after exercise.[120] Nevertheless, more frequent exercise (i.e., at least 5 days/wk) may serve to maximize both the acute glucose-lowering effect and the effect on cardiovascular risk reduction.[116]

A summary of exercise prescription and physical activity guidelines for patients with type 2 diabetes mellitus is shown in **Table 12-2**, with specific reference to the type of exercise, major goals and objectives, and the recommended intensity, frequency, and duration. It should be emphasized, however, that if these recommended levels of exercise are deemed by the patient to be unrealistic or excessive, the patient should be encouraged to achieve more moderate exercise dosages or intensities, because the primary

TABLE 12-2 Exercise Recommendations for Patients with Type 2 Diabetes Mellitus

TYPE OF EXERCISE*	MAJOR GOALS AND OBJECTIVES	INTENSITY, FREQUENCY, DURATION
Aerobic (large muscle activities)—for example, walking, jogging, stationary or outdoor cycling, swimming	Increase $\dot{V}O_2$ peak; ADLs	40%-84% $\dot{V}O_2R$[†] or HRR; 55%-89% HR max; RPE 11-16 (6-20 scale)
	Improve glycemic control and coronary risk factors	No more than 2 consecutive days without exercising; four to five sessions per week (or more) may be needed to reduce body weight and fat stores
	Decrease rate-pressure product during submaximal exercise	≥150 min/wk or ≥90 min/wk for moderate-intensity or vigorous-intensity exercise, respectively; ≥20 min per session
	Induce other cardioprotective benefits (e.g., enhanced nitric oxide vasodilator function, improved vascular reactivity, altered vascular structure, increased resistance to ventricular tachycardia and fibrillation)	For moderate-intensity activity (≤59% $\dot{V}O_2R$ or HRR and/or ≤69% HR max and/or RPE ≤13), multiple shorter periods of exercise (10- to 15-min exercise bouts) accumulated throughout the day may elicit similar (or even greater) reductions in body weight and fat stores than a single bout of the same duration
		Complement structured exercise with an increase in daily lifestyle activities (walking breaks at work, gardening, household activities); move more, sit less
Resistance training (multijoint exercises, large muscle groups, progressive)	Increase muscle strength and endurance	8-10 different exercises that work major muscle groups; weight loads gradually increased over time
	Increase ability to perform leisure and occupational activities and ADLs	≥2 times/wk
	Decrease the rate-pressure product at any given resistance (e.g., during lifting or carrying objects)	Moderate to vigorous intensity; one to four sets of 8-10 reps at a weight that cannot be lifted more than 8-10 times,[‡] or 12-15 reps at a weight that cannot be lifted more than 12-15 times (for patients with known CHD), with 1- to 2-min rest periods between sets
	Assist in the maintenance of basal metabolic rate by maintaining or increasing lean body mass over time	
Flexibility and stretching (upper and lower body ROM activities)	Improve balance and agility	Static stretches: hold for 10-30 sec
	Decrease risk of musculoskeletal and orthopedic injury	2-3 days/wk

ADLs = Activities of daily living; HR max = maximal heart rate; HRR = heart rate reserve; ROM = range of motion; RPE = rating of perceived exertion (6-20 scale); $\dot{V}O_2R$ = $\dot{V}O_2$ reserve.

*Aerobic exercise should be preceded by a warm-up (approximately 10 minutes) and followed by a cool-down (5-10 minutes) at a reduced exercise intensity (e.g., slow walking). Stretching (5-10 minutes) may be incorporated before or after the endurance exercise phase.

[†]$\dot{V}O_2$ reserve formula = ($\dot{V}O_2$ peak − $\dot{V}O_2$ rest) × 40%-84% intensity + $\dot{V}O_2$ rest, where $\dot{V}O_2$ values are expressed in METs.

[‡]Approximates 70%-84% of one repetition maximum.

beneficiaries are individuals with and without CVD who are in the least fit, least active subgroup (bottom 20%).[121,122]

The Structured Exercise Session: Special Considerations for Exercisers with Diabetes

Structured exercise training sessions should include a preliminary aerobic warm-up (approximately 10 minutes), a conditioning phase (≥20 minutes of vigorous-intensity or ≥30 minutes of moderate-intensity exercise), a cool-down (5 to 10 minutes), and ideally an optional recreational game. Stretching (5 to 10 minutes) may be incorporated before or after the conditioning or endurance exercise phase. The warm-up facilitates the transition from rest to the conditioning phase by stretching postural muscles and increasing blood flow. A gradual warm-up may also reduce the likelihood of exercise-induced ischemic responses, which can occur with sudden strenuous exertion.[123] A walking cool-down enhances venous return during recovery, decreasing the possibility of hypotension and related sequelae, and ameliorates the potential, deleterious effects of the post-exercise rise in plasma catecholamines.[124] In addition, it facilitates more rapid removal of lactic acid than stationary recovery.

For patients with diabetes with adequate blood glucose control or those who are mildly hyperglycemic, regular physical activity acutely decreases blood glucose levels and, in some patients with diabetes treated with insulin, actually reduces insulin requirements. This is because of the insulin-like effect of aerobic exercise. However, physical activity can also result in a hypoglycemic state that is the most common problem experienced by exercising patients with diabetes treated with insulin or, to a lesser extent, oral hypoglycemic drugs. Recommendations and precautionary measures to reduce the potential for exercise-related complications in patients with diabetes are shown in **Box 12-2**.

PSYCHOSOCIAL INTERVENTIONS TO SUPPORT LIFESTYLE CHANGE

Psychosocial and counseling interventions that are recommended to support lifestyle change and reduce cardiovascular risk in patients with diabetes include self-management education, screening for traits that negatively affect health behaviors, skill training targeted toward improved self-monitoring and development of coping strategies,[23] evidence-based mind-body therapies for stress reduction,[125] assessing readiness for change,[126] and motivational interviewing.[127] The literature suggests varied results when lifestyle change interventions have been used in treating patients with diabetes and CVD,[128,129] ranging from minimal to modest effects. Accordingly, the ADA recommends interventions aimed at self-management and behavior change.[23] Although the aforementioned interventions can assist in reducing health risk and mortality, this section focuses primarily on interventions that can be incorporated into day-to-day clinical practice with patients, including assessment of readiness for change, motivational interviewing, and evidence-based mind-body therapies for stress reduction.

Readiness for Change

One approach that can guide healthcare providers' interventions with patients when personal choice and behavior are key to determining outcomes is the transtheoretical model, originally proposed by Prochaska and DiClemente.[130] This model is often referred to as the *health-related behavior change model*.[131] Health-related behavior change includes behaviors that patients commonly engage in to maintain or improve their health. As **Figure 12-4** demonstrates, there are seven stages in the model. Although it is enticing to perceive the model as linear or circular, it is actually far more complex. It is possible for patients to move through varied behavioral stages in a nonlinear fashion.[131] Consequently,

BOX 12-2 Preventive Strategies for Exercisers with Diabetes

Wear proper footwear and practice good foot hygiene. Patients with diabetes, especially those with impaired nerve conduction in their feet, should use cushioned shoes (gel or air soles) and avoid high-impact activities such as running or jumping. Such activities are more likely to traumatize the feet in patients with peripheral neuropathy and precipitate vitreous hemorrhage or tractional retinal detachment in patients with active diabetic retinopathy.

Recognize that exercise in excessive heat or humidity may exacerbate the risk of heat injury in patients with diabetes with autonomic neuropathy. Associated abnormalities of the nervous system can alter cardiovascular, skin blood flow, and sweating responses to exercise in hot and humid environments, increasing the risk of heat stroke. As a general guideline, patients with diabetes should curtail outdoor exercise when the temperature exceeds 90° F, when the relative humidity exceeds 60%, or both.

Consider that diabetes increases the risk of cardiovascular events by approximately threefold (or more in women) and is associated with a higher prevalence of exertion-related myocardial ischemia, typically manifesting as angina pectoris and/or significant ST-segment depression, which can be highly arrhythmogenic. Beta blockers, in particular, may attenuate the rate-pressure product and associated cardiac demands, camouflaging or preventing signs or symptoms of myocardial ischemia. Monitor blood glucose before, during, and after physical activity when starting an exercise program. Exercise at approximately the same time each day; a good practice is to take advantage of the acute glucose-lowering effect of physical activity by timing the session at approximately 1 hour after a meal (to coincide with the peak postprandial rise in glucose).

Inject insulin in body areas where muscles are not actively recruited by exercise. For example, an inactive injection area like the abdomen should be used before walking, jogging, or stationary or outdoor bicycling.

The response to structured exercise and/or moderate-to-vigorous physical activity in the patient with diabetes taking insulin depends on a number of variables, including the adequacy of control by exogenous insulin. Accordingly, diabetes must be under adequate control before the patient begins an exercise program. A blood glucose concentration above 300 mg/dL or above 240 mg/dL with urinary ketone bodies is considered a relative contraindication to exercise participation. In patients taking insulin, consideration should be given to the ingestion of 20 to 30 g of additional carbohydrate before exercise when the preexercise blood glucose is below 100 mg/dL.

Exercising during the evening hours increases the risk of nocturnal hypoglycemia, which may occur up to 4 to 6 hours after an exercise bout. To decrease the likelihood of this response during the night (or day), the patient with diabetes may need to reduce his or her insulin dose or increase carbohydrate intake before or after exercise.

Recognize the signs and symptoms of hypoglycemia. These include heart palpitations, confusion, weakness, and visual disturbances. If hypoglycemia is left untreated, it could lead to unconsciousness or convulsions. To reduce the likelihood of complications, patients with diabetes should always carry a form of fast-acting carbohydrate (e.g., juice, candy, glucose tablets), exercise with a partner, and wear a diabetes identification tag.

Monitor for symptoms of hyperglycemia. These include excessive thirst; frequent urination; blurred vision; itchy, dry skin; and a fruity odor or breath. Hyperglycemia can lead to diabetic coma.

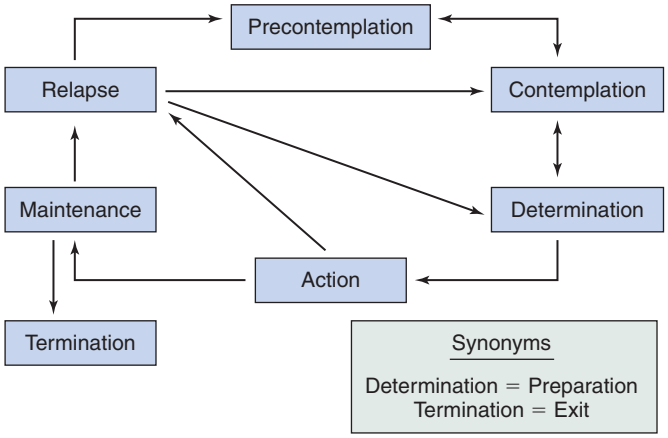


FIGURE 12-4 Stages of "readiness to change" model.

it is important to understand the components of each of the stages and how to determine at which stage patients are functioning to most appropriately intervene.

Stages of the Transtheoretical Model

Precontemplation

Patients are not thinking about making a behavioral change and likely do not even think that they have an unhealthy lifestyle and/or risk factors. The goal for healthcare providers at this stage is to help patients recognize the need for lifestyle change(s) and move them into the contemplation stage. There are several barriers for patients in this stage, which may include lack of knowledge regarding their current status or the risks for future health problems, a limited sense of self-efficacy in relation to making positive lifestyle changes, or simply feeling content with their current weight, health status, or lifestyle choices.[126,130]

Contemplation

Patients are beginning to think about making a lifestyle change but are ambivalent; they remain unsure about whether the inconvenience of changing longstanding behaviors truly outweighs the potential risk of maintaining the status quo. The goal for healthcare providers at this stage is to help patients explore the ambivalence they feel, help to solidify their desire to make a change, and move them into the preparation stage. In addition to the barriers that exist in the precontemplation stage, which may persist, a sense of indecisiveness may also be present. At this stage, patients often find it difficult to decide between continuing to engage in the same behaviors or making substantive changes that will ultimately lead to a healthier lifestyle.[126,130]

Preparation

Patients have decided to change their behavior and are planning to do so within the coming month. There are two goals for healthcare providers at this stage. The first is to help patients move into the action stage. To achieve this, healthcare providers need to help patients design an action plan that is reasonable for them. The second goal is to help patients identify barriers to making lifestyle changes. Barriers at this stage often involve the decision-making process itself. Some patients find it challenging to remain committed to making a change because they are still actively engaged in their former behaviors. Others may feel overwhelmed by the behavioral options. Healthcare providers can help patients explore these and decide which ones are most appropriate for them. It is important to remind patients that the process of behavior change is dynamic and different options can be subsequently chosen as replacement behaviors or as complementary to the behaviors recently adopted.[126,130]

Action

During the action stage, patients have begun to make lifestyle changes toward meeting an identified goal. The objectives for healthcare providers are to help patients optimize their plans for success in the short and long terms and to help them maintain the changes to create habits. There are several barriers for patients in this stage, which may include disillusionment with the process of change, a sense of failure, or a sense of overconfidence—the patient's belief that change has occurred and that potential barriers can be easily overcome. This can lead to unnerving experiences for patients when an unexpected barrier arises and they do not know how to handle it. The patient is in the action stage often for at least 6 months, and sometimes longer. Behavior change is difficult, and patients may need to be reminded that persistence regarding the target behavior is more important for long-term success than is perfection.[126,130]

Maintenance

New behaviors have become well learned and newly formed habits for patients. The goal for healthcare providers at this stage is to help ensure that patients' newly formed behaviors are stable and have become integrated into their lifestyle. Barriers within the maintenance stage arise when patients have not reached their original goal or experience major losses or stresses that can lead to resumption of previous unhealthy habits or behaviors.[126,130]

Relapse

Sometimes patients resume previous unhealthy habits or behaviors. Relapse does not occur only after patients fail maintenance, but can occur at any point during the change process. The goals for healthcare providers when relapse occurs is to identify the relapse, as well as possible triggers for it, and then reframe the "slip" or "off-target behavior" as an opportunity to learn. Patients can use relapses to identify barriers and formulate plans to address them in the future. Healthcare providers can help patients design a modified or improved plan of action in response to the relapse with the goal of overcoming the barrier and moving, once again, toward the original goal.[126,130]

Exit

Once maintenance of the new target behaviors is fully established and stable, exit occurs. At this point in time, relapse is unlikely. Patients now find themselves in a stage of precontemplation regarding the previous unhealthy behaviors. In other words, they cannot imagine wanting to go back to their former lifestyle and the unfavorable outcome(s) that were associated with their previous behaviors.[126,130]

Assessment of Stages of Change

How do healthcare providers determine the stage of change that patients are in? Engaging in a dialogue with patients and demonstrating a genuine interest in their perspective is the first step. Asking questions that are respectful, specific, and open-ended, without being judgmental, is critical. Taking time to listen to the responses carefully and then asking follow-up questions to clarify key issues from the

TABLE 12-3 Stages of Readiness to Change, with Specific Reference to Patient Beliefs and Healthcare Provider Interactions

STAGE OF CHANGE	PATIENT BELIEFS AND CHARACTERISTICS	HEALTHCARE PROVIDER INTERVENTION TECHNIQUES AND STRATEGIES
Precontemplation	Not considering change Not interested in hearing information Content to maintain status quo	Validate lack of readiness for change Provide information Personalize risk Encourage evaluation of current behavior Reassure that decision is the patient's
Contemplation	Ambivalent about change Not considering change in near future	Validate lack of readiness for change Encourage evaluation of pros and cons of current behavior Encourage evaluation of pros and cons of behavior change Identify goals for behavior change Reassure that decision is the patient's
Preparation	Seriously considering change Possibly trying out some new behaviors Planning to make change within a month	Identify goals (small ones in service of larger outcome goal) Assess importance, confidence, and motivation for behavior change Assist with identification of obstacles Assist with problem-solving to address obstacles and challenges Identify past skills and strengths that can be used and built on when change begins Identify social support network
Action	Implementing new behavior(s) Practicing new behavior(s) for 6 months	Restructure goals as needed Bolster self-efficacy; continue to build on skills and strengths Assist with identifying and implementing strategies to combat obstacles Support exploration regarding loss Provide information to reiterate long-term benefits of behavior change
Maintenance	Sustaining new behavior(s) Behavior(s) becoming habits Behaviors have been consistent for more than 6 months	Reinforce internal rewards Plan for possible relapse Develop and implement coping strategies for triggers that can lead to off-target behavior(s) Plan for support to maintain new behavior(s) as habit(s)
Relapse	Resuming old behavior(s)	Identify triggers for relapse Develop and implement coping strategies Reassess importance, confidence, and motivation for behavior change Discuss pros and cons of relapse behavior(s) Discuss pros and cons of behavior change
Exit	New behavior(s) now considered habit(s); natural part of daily life	Continue to support behaviors and coping strategies as needed Use success with behavior change as a strength to make other unrelated behavior changes as needed

patients' perspective helps develop a mutual understanding of the issue and the level of interest patients have regarding behavior change.[126,130] **Table 12-3** provides an overview of the stages of change, typical patient beliefs or characteristics at each stage, and methods of intervening, which healthcare providers can use to support movement through the stages and eventual behavior change.

Motivational Interviewing

The effectiveness of motivational interviewing as a therapeutic approach to address diabetes, cardiovascular health, and other clinically relevant lifestyle changes has yielded varying results, from strong evidence for to low levels of sustained behavior change.[132,133] Nevertheless, there remains enthusiasm for motivational interviewing within healthcare provider–patient interactions in a variety of settings.[134–137]

Motivational interviewing is based on the notion that all behavior is motivated, including the ambivalence that people experience when deciding whether to engage in a particular behavior or not. It does not focus on the action of change itself, but rather on the motivation to make change(s).[138–140] This type of talk therapy was initially developed as a method to treat patients with addictive behaviors and, once it was shown to be effective, was expanded to address other health-related behaviors.[139,140] The underlying power of this therapeutic approach is that patients talk themselves into changing behavior, rather than having it suggested or advised by others. Although motivational interviewing is not a particular method of interacting with patients, the spirit, principles, and skills it promotes offers healthcare providers a way of focusing on building rapport with patients and collaborating with them to identify, examine, and reduce or resolve the ambivalence they may have in relation to behavior change through a variety of techniques.[138–141]

"Spirit" of Motivational Interviewing

Collaboration

To establish a partnership, it is important to develop a genuine, comfortable environment in which patients do not feel judged. This approach requires more listening than talking, and restating what the healthcare provider hears from the patient, so that the patient feels that his or her perspective is valued. The therapeutic process is focused on developing a mutual understanding, which may not always include agreement.[127,131,140]

Evocation

Drawing out the patients' beliefs and motivations regarding behavior change is key to setting the stage for long-term change. The role of healthcare providers is to draw out patients' motivations and skills for behavior change.[127,131,140]

Autonomy

Emphasizing the right of patients to make their own decisions but also empowering them to maintain responsibility for implementing behavior change is critical, but sometimes



overwhelming. When multiple changes may be necessary to reach an identified health goal (e.g., control of diabetes signs and symptoms, weight loss), it often helps if patients determine which behavior to focus on first.[127,131,140]

Principles of Motivational Interviewing

Express Empathy

It is important to be able to express understanding in a manner that enables patients to feel heard and understood, in a nonjudgmental manner that reflects the viewpoints and experiences of the patient.[127,131,134,140,141]

Support Self-Efficacy

Motivational interviewing is a strengths-based approach that operates from the perspective that patients have within themselves the capability to change behaviors successfully. Healthcare providers support self-efficacy by focusing on previous successes and highlighting skills and strengths that patients already possess. To this end, healthcare providers can suggest skills and strengths that can be used or built on, as change is being considered, planned, and implemented. In addition, allowing patients to set their own agenda for change will support self-efficacy. For example, when considering multiple lifestyle changes that might be necessary for successful management of diabetes (e.g., self-monitoring of glucose levels, changing eating habits, increasing physical activity, reducing stress), allowing patients to determine which change to make first empowers them and increases the likelihood of the behavior change being sustained over time.[127,131,140–142]

Roll with Resistance

Resistance is not a part of the personality or character of patients. Instead, it is a manifestation of the process going on between providers and patients, as well as the ambivalence that is felt or experienced by patients when they contemplate making behavioral changes. When patients argue against, challenge, or discount information presented by providers or interrupt and/or talk over providers, they are likely demonstrating resistance to hearing or truly accepting the need for change. Resistance also presents itself in the form of denial, when patients deny they have lifestyle deficits, blame others for the problem, or minimize the potential negative impact of the habit at hand. Finally, resistance may occur when patients overtly ignore what providers say, do not respond, or sidetrack, discussing issues unrelated to what providers have just articulated. Rather than engaging in a head-to-head confrontation, or meeting force with force, rolling with resistance involves use of techniques that allow the scenario to dissipate. Some of the techniques that enable this to occur are described later.[127,131,140,141]

Develop Discrepancy

When discussing change possibilities, helping to develop differences among the beliefs of patients regarding their health, current behaviors, and desired goal(s) may assist them to move along the readiness to change continuum. If an agenda is set and self-efficacy is supported, discrepancies among patients' understanding, beliefs, and goals often come to light. Essentially, motivation for change occurs when individuals perceive a discrepancy between where they are and where they want to be. Once discrepancies are identified and reflected back to patients, carefully crafted questions can be asked to help the patients understand the mismatch and empower them to move toward behavior change.[127,131,140,142]

Interviewing Skills and Strategies

Motivational interviewing uses varied interviewing skills and strategies that are taught as basic communication skills for developing strong healthcare provider–patient relationships. The acronym OARS can cue healthcare providers to implement the most commonly used skills and strategies, including open-ended questions, affirmations, reflections, and summaries.[140]

- *Open-ended questions:* Asking questions that cannot be answered easily with a "yes/no" or limited response can lead to obtaining useful information from patients that allows healthcare providers to develop a better understanding of their concerns and perspectives. Open-ended questions encourage patients to talk and provide personal viewpoints. These types of questions often begin with what, how, why, or could.[131,140,141]
- *Affirmations:* Statements that highlight patient strengths can be a useful tool to support behavior change. Pointing out positive traits or characteristics to patients empowers them to build on existing skills and strengths. Affirmations may include complimenting effort, acknowledging small successes, or stating appreciation.[131,140,141]
- *Reflections:* Reflective listening involves recognizing key words or feelings expressed by patients and using them to paraphrase what was heard. The main ideas or concepts reflected back to patients should represent their point of view, not those of the healthcare provider. Reflective listening accomplishes two goals: first, it enables providers to express empathy and demonstrate understanding of patients' perspectives; second, healthcare providers can use reflective listening to identity ambivalence regarding behavior change and guide patients toward resolving their uncertainty.[131,140,141]
- *Summaries:* Recapping what has occurred in healthcare provider–patient interactions communicates interest and understanding and can lead to movement away from previous unhealthy behaviors.[131,140,141]

In addition to OARS, other skills are also useful within the context of motivational interviewing. Establishing structure, or setting an agenda for the visit, helps providers to focus on readiness for change and appropriate behavior change processes.[127] The recommended structure is to ask a question that determines readiness for change, listen to patients' responses, and provide information that might help patients move along the change continuum. Once healthcare providers have shared information with patients, they can then ask patients to share their understanding or interpretation of the information that was provided.[131]

Other important strategies when engaged in motivational interviewing include assessing the importance of the change being discussed, along with the confidence level of patients in their ability to make the change, and finally attempting to increase patients' motivation for change.[127,135] Readiness to change is influenced by how important individuals perceive change to be, as well as how confident they are that they can make the change.

For healthcare providers, assessing importance and confidence regarding a mutually agreeable change goal are necessary. For example, "On a scale of 1 to 10, with 10 being the highest, how important is it for you to keep your blood sugar level within the normal range each day?" In

TABLE 12-4 Stages of Readiness to Change with Sample Motivational Interviewing Questions to Favorably Modify Patient's Behaviors (e.g., Weight Reduction)

STAGE OF CHANGE	PATIENT STATEMENT OR BELIEF	HEALTHCARE PROVIDER INTERVENTION
Precontemplation	I am comfortable at my current weight.	I am worried about the effect that your weight is having on other health factors, and although you aren't ready to discuss weight loss strategies today, I would like to discuss this issue the next time we meet, okay?
Contemplation	I would like to lose weight, but I don't know where to begin.	What do you like least about your current habits? Which habit can you see yourself changing first? How might you set things up in your life to be able to do so?
Preparation	I am going to buy a gym membership next month so that I can start exercising 3 days per week.	It sounds like you have decided that physical activity is the most important thing to change right now. What can you do now to help ensure that you will be able to go to the gym 3 days per week like you stated you want to do?
Action	I have gotten all of the junk food out of the house so that I can focus on eating healthier foods without any temptations.	That's wonderful. What are some other barriers that you find get in the way of making healthy eating choices on a consistent basis?
Maintenance	I have been going to the gym 3-5 times weekly and am no longer eating fast food. I have been able to sustain these behaviors for the past 6 months.	It sounds like you have been able to maintain positive changes with your eating habits and physical activity for quite a long time. Do you worry about particular triggers that might tempt you to engage in old, unhealthy behaviors? If so, have you thought about how to combat the triggers if they arise?
Relapse	Things got so busy at work that I started stopping for fast food on my way home from work and I have regained some of the weight I lost this past year.	It sounds like you were able to identify the trigger that led you off target. What are some things you can do to balance work demands while continuing to engage in the healthier new behaviors you have been working toward creating as habits that you would like to last for life?
Exit	I have maintained my current weight for the past 2 years and I don't see myself ever going back to my old ways.	If you were giving someone else advice regarding how to maintain consistent healthy choices, what would you tell him or her?

assessing the level of importance for making a change, it is common for resistance to arise. If a patient rates the level of importance below 7, it suggests that the healthcare provider may be moving too quickly in the approach.

Once an importance level has been established, it is also possible to use the rating to increase the patient's motivation level to engage in change by asking him or her to elaborate on why he or she rated the importance at the particular level that was chosen. Whether the rating is higher or lower in the range, questions can be asked to solidify or shift the rating upward. For example, "Although you indicated that you want to pay closer attention to the fluctuation in your blood sugar throughout the day, when I asked you to rate the importance of monitoring your blood sugars daily, you rated the importance as 6. What would it take to increase the importance level to a 7 or 8?"

Similar methods can be used to determine patients' confidence level for making a behavioral change. Once again, a confidence rating below 7 suggests the need to determine what would be necessary to increase the level of confidence that change can be made successfully. Without a higher confidence level, patients are likely to fail in their effort to change behaviors.

Using Change Talk in Motivational Interviewing

Change talk includes statements made by patients that suggest consideration of change, motivation for change, or commitment to change. The acronym DARN CAT can help healthcare providers to remember the different types of statements and their meanings. The first four types of change talk, represented by *DARN*, reflect precommitment to change (desire, ability, reason, need). There may be conflict or ambivalence noted between statement types, which are often paired together with the connector word *but*. For example, "I want to [desire], *but* I can't [ability]".[140,141] The last three types of change talk, represented by *CAT*, reflect commitment to change (commitment, activation, taking steps).

In summary, motivational interviewing offers healthcare providers a therapeutic approach to health-related behavior change issues that allows for increased mutual understanding regarding patients' perceptions and experience, as well as methods to increase importance, confidence, and motivation regarding making behavioral changes and developing an action plan to achieve long-term success.

Table 12-4 combines the transtheoretical model of stages of change and motivational interviewing strategies to illustrate how the two models can be used in conjunction with each other.[143] Weight loss goals are used as examples for interventions for all stages.

Evidenced-Based Mind-Body Therapies

Research demonstrates reduction in risk for both cardiovascular events and mortality when stress reduction techniques are used by patients.[125] Yet traditional medicine often falls short in offering integrative approaches for stress reduction. Healthcare providers can recommend options such as meditation, yoga, mindfulness-based stress reduction, pet ownership, guided imagery, biofeedback, and tai chi, or combinations thereof, all of which are associated with significant reductions in stress and stress-related illnesses.[125,142] Many of these methods can be taught by healthcare providers, learned in settings identified by healthcare providers, and offered to patients at risk, including those with diabetes.

SUMMARY

The treatment of CVD has evolved from simple lifestyle modifications in the 1960s, largely focused on a "prudent diet" and regular exercise, to an array of costly medical and revascularization interventions that too often fail to address the underlying causes—poor dietary habits, physical inactivity, and cigarette smoking. The INTERHEART

study examined the risk factors associated with first acute myocardial infarction in 52 countries, including 15,152 patients and 14,820 controls.[144] Five risk factors (abnormal lipids, smoking, hypertension, diabetes mellitus, abdominal obesity) accounted for approximately 80% of the population attributable risk in men and women. Similarly, Khot and colleagues[145] and Greenland and colleagues[146] examined data from 14 randomized clinical trials and three prospective cohort studies and reported that more than 80% of patients who developed CHD and 87% or more of patients who experienced a fatal coronary event had antecedent exposure to at least one of the four conventional cardiovascular risk factors (cigarette smoking, dyslipidemia, hypertension, diabetes mellitus). Collectively, these data and other recent reports[147,148] suggest that a more rigorous focus on these risk factors and the lifestyle behaviors that promote them has great potential to reduce the burden of atherosclerotic CVD. Added benefits include a reduction in angina symptoms, decreases in exercise-induced signs or symptoms of myocardial ischemia, fewer recurrent cardiac events, an improved quality of life, and diminished need for coronary revascularization.

The issue is not information but methods, motivation, and behavioral changes.[149] Accordingly, patients with diabetes should be directed toward comprehensive programs designed to change behavior and facilitate cardiovascular risk reduction, with use of individually tailored interventions to circumvent or attenuate barriers to participation and adherence. The challenge is yours!

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13 Effect of Glucose Management on Coronary Heart Disease Risk in Patients with Diabetes

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Coronary heart disease (CHD) is the most common vascular complication of diabetes. Because elevated glucose defines diabetes and because diabetes is a well-recognized risk factor for CHD, strategies that lower glucose should theoretically reduce the risk of CHD events in diabetes. In reality, the relationship between glucose-lowering strategies and cardiovascular outcomes is complex and suggests that the impact of interventions on patient outcomes cannot be easily predicted from the effects of interventions on surrogate measures (such as glucose or hemoglobin A1c, HbA1c). Indeed, CHD can precede the development of diabetes, and some have suggested that both conditions (CHD and diabetes) have common genetic and environmental roots and spring from a "common soil" (**Fig. 13-1**) (see also Chapters 2, 8, and 9).[1] This chapter describes the epidemiologic relationship between glucose and CHD, reviews clinical trial evidence of the effects of glucose lowering on CHD outcomes, discusses the benefits and risks of glucose lowering with specific medications and in specific patient populations, and concludes with implications for clinical practice.

CHANGING EPIDEMIOLOGY OF DIABETES AND CORONARY HEART DISEASE

The general incidence and prevalence of CHD have declined in the United States in the last several decades, and this decline has been accompanied by a decline in CHD-related mortality.[2] These trends have been attributed to better cardiovascular risk factor control and treatment during and after acute coronary syndromes over time, primarily with the use of statin medications, blood pressure management, and anti-platelet therapies. In contrast to CHD trends, the incidence and prevalence of diabetes have been steadily increasing over time, with the disease now affecting close to a third of older U.S. adults (65 years or older) (see also Chapter 1).[3,4] In addition, adults with diabetes are living longer.[5] As a result, the burden of CHD attributable to diabetes is increasing (see also Chapter 7).[6] These changes in the epidemiology of diabetes and CHD have important implications. First, strategies that mitigate the risk of CHD in diabetes patients will be of growing importance because heart disease is increasingly a complication of diabetes. Second, these strategies will be applied to an aging population with a high comorbidity burden and at higher risk for adverse effects of therapy.

EPIDEMIOLOGIC RELATIONSHIP OF GLUCOSE WITH CORONARY HEART DISEASE

Multiple studies have assessed the relationship between various glucose parameters—fasting glucose, 2-hour glucose during an oral glucose tolerance test, or HbA1c levels—and the risk of CHD in populations with and without diabetes. Most of this work suggests a continuous relationship between measures of glycemia and CHD risk.

Several studies and a metaregression analysis have shown that in nondiabetic populations, there is a graded relationship between initial fasting and postprandial glucose levels and subsequent occurrence of cardiovascular events over 12 years of follow-up.[7] The association is apparent even at levels below the diabetic thresholds. However, because HbA1c is the preferred test for monitoring blood glucose control during the chronic management of diabetes, data summarized here will be predominantly based on this glycemic parameter.

In the large prospective population study of Norfolk, in the United Kingdom, HbA1c and cardiovascular risk factors were assessed from 1995 to 1997, and cardiovascular disease events and mortality were examined during the next 6 to 8 years of follow-up.[8] The relationship between HbA1c and cardiovascular disease and total mortality was continuous and apparent even among persons without diabetes. The risk was lowest among persons with HbA1c below 5% and increased thereafter throughout the range of nondiabetic HbA1c levels up to 6.9%. Each one percentage point increase in HbA1c above 5% was associated with a 20% to

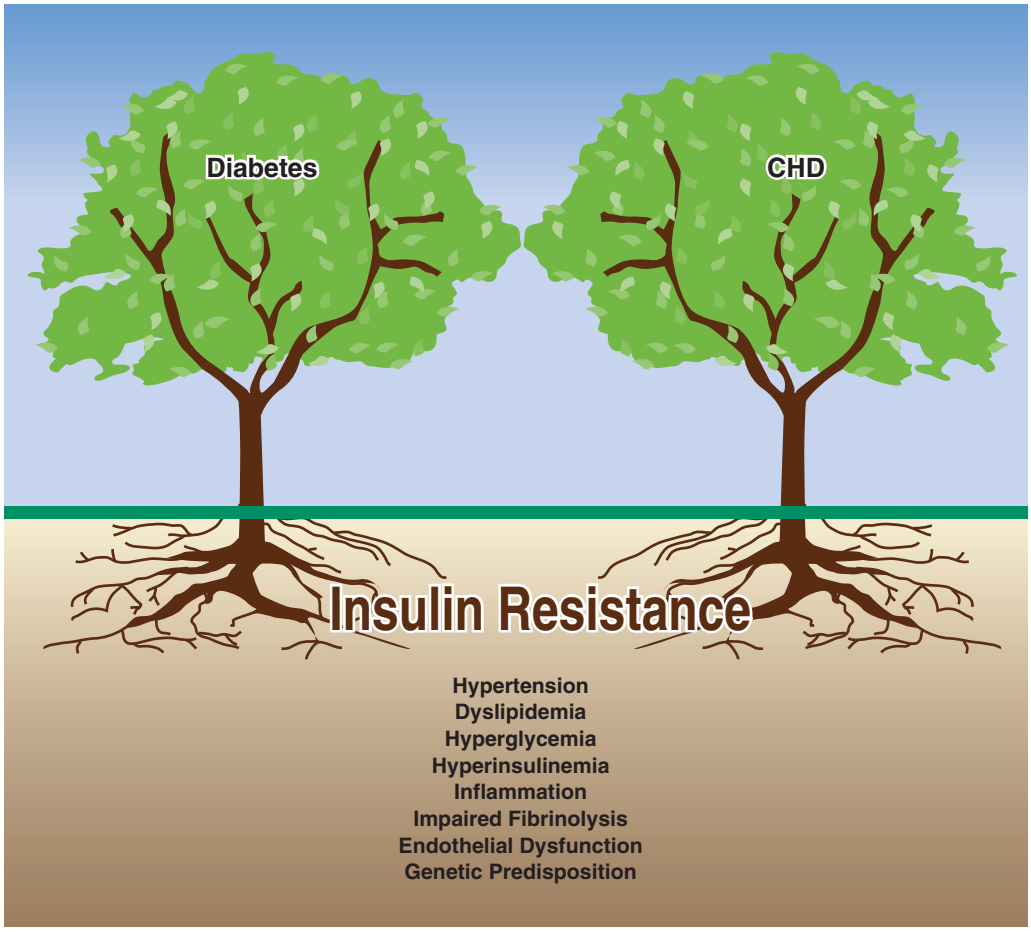


FIGURE 13-1 The "common soil" hypothesis of diabetes and coronary heart disease (CHD).

25% increase in the relative risk for CHD among men and women in age- and risk-factor adjusted models. Moreover, when known diabetes status and HbA1c concentration were included in the same model, diabetes was no longer a significant independent predictor of CHD, suggesting that the increased risk of CHD in dysglycemic states is mediated through hyperglycemia itself.

The prognostic value of HbA1c was also assessed in the Atherosclerosis Risk in Communities (ARIC) study of U.S. adults without a prior history of diabetes or cardiovascular disease and with up to 15 years of follow-up.[9] Similar to the observations from the Norfolk study, the risk for CHD increased with higher HbA1c values in a continuous fashion independent of classic cardiovascular risk factors. When compared with study participants with HbA1c of 5% to less than 5.5% (the reference range), the hazard ratio (HR) for CHD was increased 23% in those with HbA1c of 5.5% to less than 6%, 78% for HbA1c of 6% to less than 6.5%, and 95% for HbA1c of 6.5% or higher. Although, clearly, the causal role of glucose in the development of CHD could not be evaluated in this epidemiologic study, the findings suggest that HbA1c, even in the nondiabetic range, can be a useful independent marker of cardiovascular risk.

Although the association between HbA1c level and CHD may be prognostically important in nondiabetic individuals, to understand the effect of glucose lowering on CHD risk we must examine data in patients with diabetes. A prospective observational study of type 2 diabetes patients enrolled in the United Kingdom Prospective Diabetes Study (UKPDS) examined the relationship between HbA1c and cardiovascular complications. They found that each 1% increase in the updated HbA1c was associated with a 14% relative risk increase for myocardial infarction (MI; **Fig. 13-2**).[10] A meta-analysis of 13 prospective cohort studies of HbA1c and cardiovascular disease in persons with diabetes (type 1 or 2) suggested that chronic hyperglycemia is associated with an increased risk for cardiovascular disease. The pooled relative risk for cardiovascular disease associated with a 1% increase in HbA1c was 1.18. In a subgroup of six studies conducted in patients with type 2 diabetes, a 1% increase in HbA1c was associated with a 13% increased relative risk for CHD.[11] The inclusion criteria for the meta-analysis did not specify pharmacologic treatment for diabetes; rather, these were observational studies involving patients on both medication and diet therapy. These results suggest a moderate increase in cardiovascular risk with increasing HbA1c in diabetic adults. However, the meta-analysis relied on small studies with some suggestion of heterogeneity of effects that could not be explored in detail.

One large analysis examined data from the U.K. General Practice Research Database (GPRD) on 27,965 patients with type 2 diabetes whose oral monotherapy was intensified to oral combination therapy, and 20,005 whose oral therapy was intensified to include insulin.[12] The primary and secondary outcomes for the two cohorts were all-cause mortality and major cardiovascular events, respectively, over the mean follow-up of 4.5 years. HbA1c in the study was based on the mean of any values recorded between the therapeutic

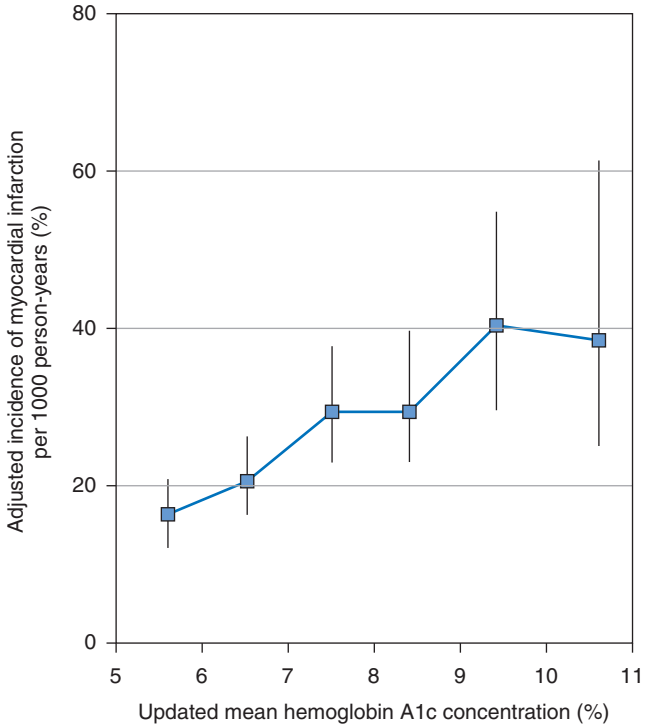


FIGURE 13-2 **Epidemiologic relationship between hemoglobin A1c and cardiovascular events.** *(Modified from Stratton et al. BMJ 2000.[10])*

switch and death or date of censor. In combined cohort analysis, the HbA1c decile with a median value of 7.5% (interquartile range 7.5% to 7.6%) was associated with the lowest mortality and the lowest progression to large-vessel disease among those without prior history of cardiovascular events. Higher and lower HbA1c values were associated with an increased risk, and the pattern of risk was U shaped. In the oral combination therapy group, a wider range of HbA1c values was safe with respect to mortality risk (median HbA1c 6.9% to 8.9%), whereas this range was narrower for patients on insulin (median HbA1c 7.5% to 8.1%). In addition, the use of insulin was associated with an approximately 50% higher hazard of mortality compared with the use of oral agents. Although no evidence supports a direct cardiotoxic effect of insulin in type 2 diabetes, it is certainly possible that age, comorbidities, and diabetes duration may be related to the decision to initiate insulin as well as to the higher mortality risk. The findings from this study differ significantly from the graded, continuous epidemiologic relationships between HbA1c and cardiovascular outcomes in individuals without diabetes. In nondiabetic populations, lower HbA1c values predict better outcomes without a clear threshold, but the data from treated patients with diabetes suggest that there may be a risk associated with achieving near-normal glycemia.

Another retrospective cohort study, this time performed in the United States, confirmed the results of the GPRD analysis. Here, data from 71,092 patients with type 2 diabetes age 60 years or older within the Kaiser Permanente Northern California system were analyzed to examine the association between baseline HbA1c level and subsequent nonfatal complications (metabolic, microvascular, and cardiovascular events) and mortality.[13] The authors found a similar U-shaped relationship between HbA1c level and mortality, with higher risk in those with HbA1c below 6% and 10% or higher in the adjusted models. In contrast, however, the relationship between HbA1c and cardiovascular events was continuous with increasing risk above HbA1c of 6%. Integrating all of the outcomes together, the "optimal" HbA1c range identified by this study lay somewhere in the 6% to 7.9% range. As in the GPRD study, the analysis added important information about optimal glycemic targets in diabetes, suggesting that achievement of low glycemic levels may provide benefits (such as lower risk of CHD), but that very low levels of glycemia may be associated with harm (e.g., higher mortality risk). A third study, this involving all adults with type 2 diabetes drawn from the Kaiser Permanente Southern California system, showed a U-shaped relationship between HbA1c and cardiovascular events, with HbA1c levels of 6% or lower and greater than 8% associated with an increased risk of cardiovascular events.[14] Whether or not low HbA1c levels are a marker of sicker patients or a mediator of harm remains highly debatable. Moreover, whether this phenomenon is actually directly attributable to lower than desirable glycemia or to adverse effects of the medications clinicians use to achieve this range is not clear. Randomized clinical trials can test the effects of interventions directly on patient outcomes and may be able to provide greater insight into the effect of glucose lowering on CHD events.

TRIALS OF GLUCOSE-LOWERING INTERVENTIONS

The landmark trial in type 2 diabetes that investigated the effect of intensive glucose lowering on microvascular and macrovascular outcomes was the UKPDS. The trial was begun in 1977 and the results were published in 1998. In this trial, 3867 patients with newly diagnosed type 2 diabetes (median age 54) were randomized to intensive treatment with sulfonylureas (chlorpropamide, glibenclamide (glyburide in the U.S.), or glipizide) or with insulin, versus conventional therapy with diet alone.[15] The median HbA1c level in the intensive group during the course of the trial was 7%, versus 7.9% in the conventional arm. Three separate aggregate endpoints were studied over the 10 years of follow-up. The risk in the intensive group was 12% lower for any diabetes-related endpoint ($P=0.03$), which included both macrovascular and microvascular events as well as metabolic complications; not significantly lower for any diabetes-related death (−10%, $P=0.34$); and not significantly lower for mortality (−6%, $P=0.44$), compared with patients treated with diet only. The reduction in diabetes-related endpoints was driven by a 25% risk reduction in microvascular events, and the reduction in MI did not reach statistical significance (−16%, $P=0.052$). A subgroup of UKPDS patients who were overweight (>120% ideal body weight) were randomized either to intensive therapy with metformin (n = 342, median HbA1c 7.4%) or conventional diet therapy (n = 411, median HbA1c 8%).[16] In this subset of patients, treatment with metformin was associated with a 32% reduction in any diabetes-related endpoint ($P=0.002$), 42% reduction in diabetes-related death ($P=0.017$), and 36% reduction in mortality ($P=0.011$). In this cohort of patients treated with metformin, there was a significant 39% reduction in MI ($P=0.01$) (**Fig. 13-3**). In summary, the UKPDS trial established that intensive glucose control reduces the risk of microvascular complications in patients with newly

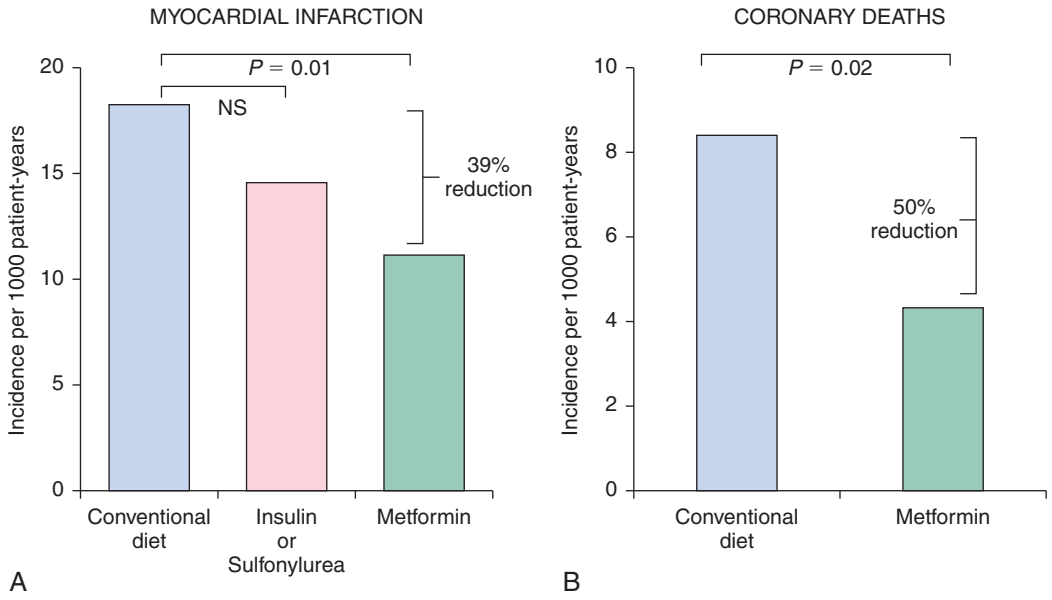


FIGURE 13-3 Results of the UKPDS trial with respect to myocardial infarction and coronary deaths. NS = Non significant. *(Modified from Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes [UKPDS 34]. UK Prospective Diabetes Study [UKPDS] Group,* Lancet *352:854, 1998).*

diagnosed type 2 diabetes, but suggested that macrovascular benefits may be confined to overweight patients treated with metformin therapy.

After the UKPDS trial was completed, study participants and their clinicians were advised to lower levels of blood glucose as much as possible, and patients returned to community or hospital-based diabetes care according to their clinical needs without any attempts to maintain previously randomized therapies. In the 10-year post-trial monitoring study of patients who survived to the end of the UKDPS trial, HbA1c levels were no longer different between the original intensive and conventional arms (approximately 8% at the end of the post-trial monitoring period).[17] In the sulfonylurea-insulin group, relative risk reductions for diabetes-related endpoints persisted, whereas significant risk reductions for MI (15%, $P=0.010$) and mortality (13%, $P=0.007$) emerged over time. In the metformin group, relative risk reductions persisted for any diabetes-related endpoint, MI (33%, $P=0.005$), and mortality (27%, $P=0.002$). These observations suggest a modest but sustained effect of intensive glucose lowering on cardiovascular events, but only after many years of follow-up. Whether the effect is confined to patients with newly diagnosed type 2 diabetes or whether it reflects the long period of time required to significantly affect subsequent atherosclerotic outcomes is not entirely clear.

Even before the cardiovascular benefits of intensive glucose therapy emerged in the long-term follow-up of the UKPDS trial, guidelines recommended a target HbA1c level of 7% or less in most patients. This was primarily driven by the expectation of microvascular benefits, albeit with uncertainty over the effects on macrovascular events. To settle the questions about the role of intensive glucose therapy in type 2 diabetes, three randomized controlled trials were specifically designed to examine the impact of targeting near-normal glycemia on cardiovascular risk. The HbA1c targets were set low because of the continuous epidemiologic relationship of glucose with cardiovascular risk, suggesting that perhaps much lower glucose levels need to be achieved for a significant benefit to emerge. The three trials all recruited participants with type 2 diabetes who had either a history of or multiple risk factors for cardiovascular disease, thus ensuring adequate event rates to study the effects of the interventions. Participants were therefore quite distinct from patients in the UKPDS trial—they were older, had a longer duration of diabetes, and had a greater comorbidity burden.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 10,251 patients (mean age 62, median baseline HbA1c 8.1%, 35% with history of prior cardiovascular event) to intensive glucose therapy (targeting HbA1c <6%, median achieved HbA1c 6.4%) versus conventional therapy (targeting HbA1c 7% to 7.9%, median achieved HbA1c 7.5%).[18] This trial was stopped prematurely after a mean follow-up of 3.5 years because of a higher mortality rate in the intensive therapy group compared with the control arm (HR 1.22, $P=0.04$). The primary endpoint of the trial, major cardiovascular events, was not significantly reduced (HR 0.90, $P=0.16$), although the rate of nonfatal MI was lower in the intensive therapy group (HR 0.76, $P=0.004$). To date, analyses have not identified any clear explanation for the higher mortality risk associated with the intensive glucose-lowering strategy. In the intensive therapy group, a median HbA1c level of 6.4% was rapidly achieved and maintained, but subsequent post hoc analyses implicated factors associated with persistently higher HbA1c, rather than low HbA1c, as likely contributors to the increased mortality risk.[19] In addition, rates of serious hypoglycemia requiring medical assistance were threefold higher in the intensive group than during standard therapy (10.5% versus 3.5%, $P<0.001$). Subsequent retrospective epidemiologic analyses of ACCORD have suggested, however, that severe hypoglycemia may not, in fact, account for the difference in mortality between the two study arms.[20] Although hypoglycemia was associated with increased mortality within each randomized group, the risk of death was actually lower in participants experiencing hypoglycemia in the intensive arm than in participants with hypoglycemia in the standard arm. Other explanations, such as the particular medication combinations or undetected medication

interactions, have also been proposed, but no particular medication class has been implicated thus far. In the end, the explanation for the increased mortality may never be known, but the findings have led to a growing recognition that intensive glucose lowering may be associated with some benefits but also important risks.

Subsequent follow-up of the participants from the ACCORD trial, up to the originally planned 5 years, showed persistently increased mortality rates in the intensive therapy group (HR 1.19, $P=0.02$), but still lower rates of nonfatal MI (HR 0.82, $P=0.01$).[21] Given these findings, strategies used in the ACCORD study targeting an HbA1c below 6% are not recommended for patients with advanced type 2 diabetes and established macrovascular complications or multiple risk factors for cardiovascular events.

At the same time the ACCORD study was published, results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial also became available.[22] In this trial, 11,140 patients with type 2 diabetes (mean age 66, median baseline HbA1c 7.2%, 32% with history of major macrovascular disease) were randomized to intensive therapy (preferentially with the sulfonylurea gliclazide, targeting HbA1c $\leq$6.5%, with mean achieved HbA1c 6.5%) or to standard therapy (HbA1c goal according to local guidelines, mean achieved HbA1c 7.3%). After a median follow-up of 5 years, there was a reduction in the primary outcome of the study, which was a composite of microvascular and macrovascular events (HR 0.90, $P=0.01$), and this was almost entirely driven by effects on intermediate markers of nephropathy. There was no significant effect with respect to major cardiovascular events (HR 0.94, $P=0.32$) in ADVANCE, but also no increase in mortality (HR 0.93, $P=0.28$) as in ACCORD. Investigators of ADVANCE specifically examined various subgroups at potentially increased risk of death, but none were identified. Overall, the trial findings suggest a modest improvement in markers of microvascular complications with intensive treatment, but no significant benefit gained with respect to CHD endpoints.

One additional trial confirmed the lack of significant benefit of intensive glucose lowering on major cardiovascular events, the Veterans Affairs Diabetes Trial (VADT). In this study of 1791 U.S. military veterans with type 2 diabetes (mean age 60, median baseline HbA1c 9.4%, 40% with prior history of cardiovascular events), participants were randomized to intensive glucose or standard therapy using a combination of agents, with a goal of achieving an absolute reduction in HbA1c of 1.5% in the intensive versus the standard arm. Median HbA1c levels achieved were 6.9% versus 8.4% in the intensive and standard groups, respectively, over a median follow-up of 5.6 years. There was no significant benefit with respect to the primary composite outcome, of cardiovascular events (HR 0.88, $P=0.14$), the individual outcome of death from any cause, nor any difference with respect to most microvascular complications (no changes in retinopathy, new neuropathy, or doubling of creatinine, but reduction in some albuminuria-based endpoints). In this study of patients with advanced type 2 diabetes, other cardiovascular risk factors were well controlled, and differences in HbA1c levels between the two groups were maintained. However, overall, the benefit of decreasing HbA1c from 8.4% to 6.9% was minimal, except in the progression of albuminuria, an intermediate marker with uncertain implications for long-term renal risk.

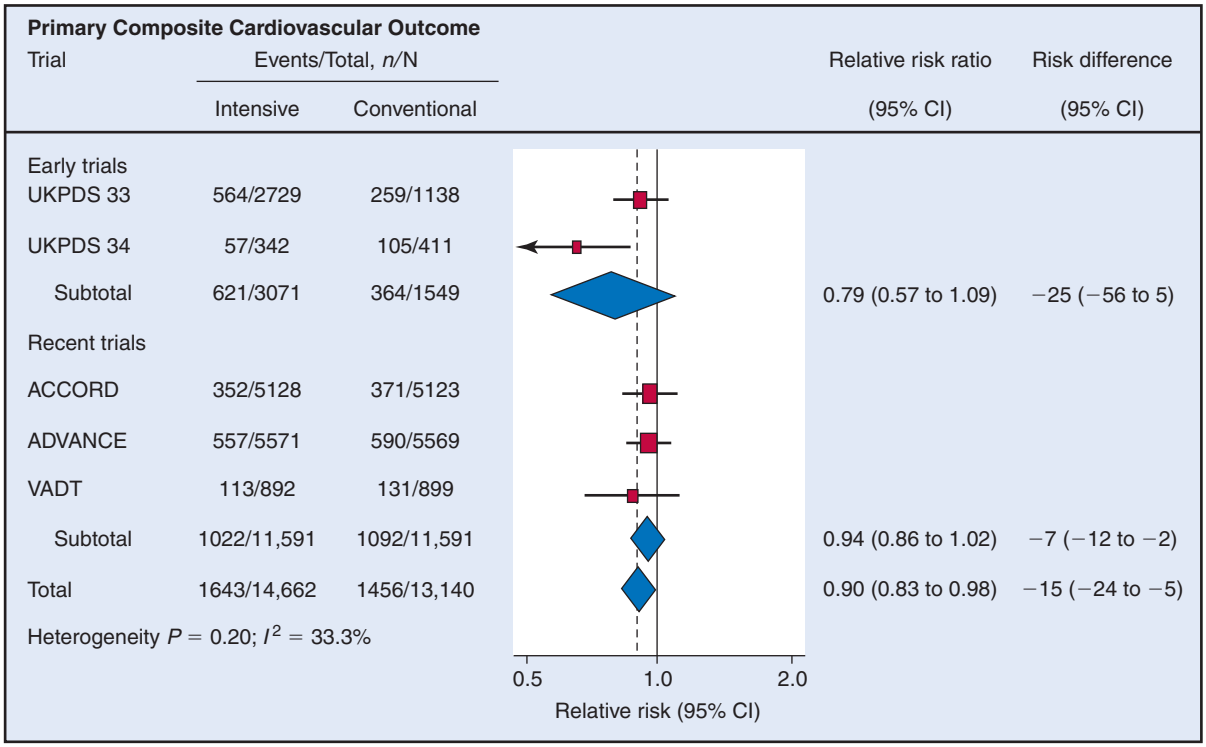
Multiple meta-analyses have followed the three randomized controlled trials described earlier to determine whether pooling results of existing studies will illuminate our understanding of these relationships (**Fig. 13-4**). Although these analyses sometimes included studies of different intent (not necessarily glucose-lowering per se) and with variable patient characteristics (newly diagnosed versus advanced diabetic patients), they consistently show a modest, although significant, reduction of approximately 15% in the risk for nonfatal MI, but no impact on mortality or cardiovascular death.[23–28] Moreover, all of these studies show that the risk for severe hypoglycemia with intensive glucose therapy is more than doubled.

Why have these large randomized controlled trials failed to show that intensive glucose lowering improves cardiovascular outcomes when the epidemiologic relationship between glycemia and cardiovascular events is so convincing? Many of the expectations for reduction in risk may have arisen from the effects of statin medications on major adverse cardiovascular events (MACEs) in early trials. A strong epidemiologic association between cholesterol and CHD exists, and interventional studies show a 23% relative reduction in risk achieved for every 1 mmol/L (38 mg/dL) of cholesterol lowering. Glycemia is a much weaker risk factor for CHD than cholesterol, but the assumption has been that some degree of risk reduction should result from glucose lowering. However, it is clear that the simple arithmetic (lower the level of a risk factor and cardiovascular events will naturally follow) does not apply in the case of glycemia. There may be a modest reduction in nonfatal MI, but overall disappointing results with respect to mortality and the composite of major cardiovascular events. Several potential explanations can be proposed: significant adverse effects of glucose therapy may counterbalance possible benefits, effects of glucose lowering applied in advanced diabetes may be too late to prevent atherosclerotic events, or the impact of glucose lowering may take a longer time to materialize than the 5 to 7 years assessed in most clinical trials. Regardless of the reasons, currently available therapies tested in these studies do not appear to constitute a "magic bullet" for the increased cardiovascular morbidity of diabetes.

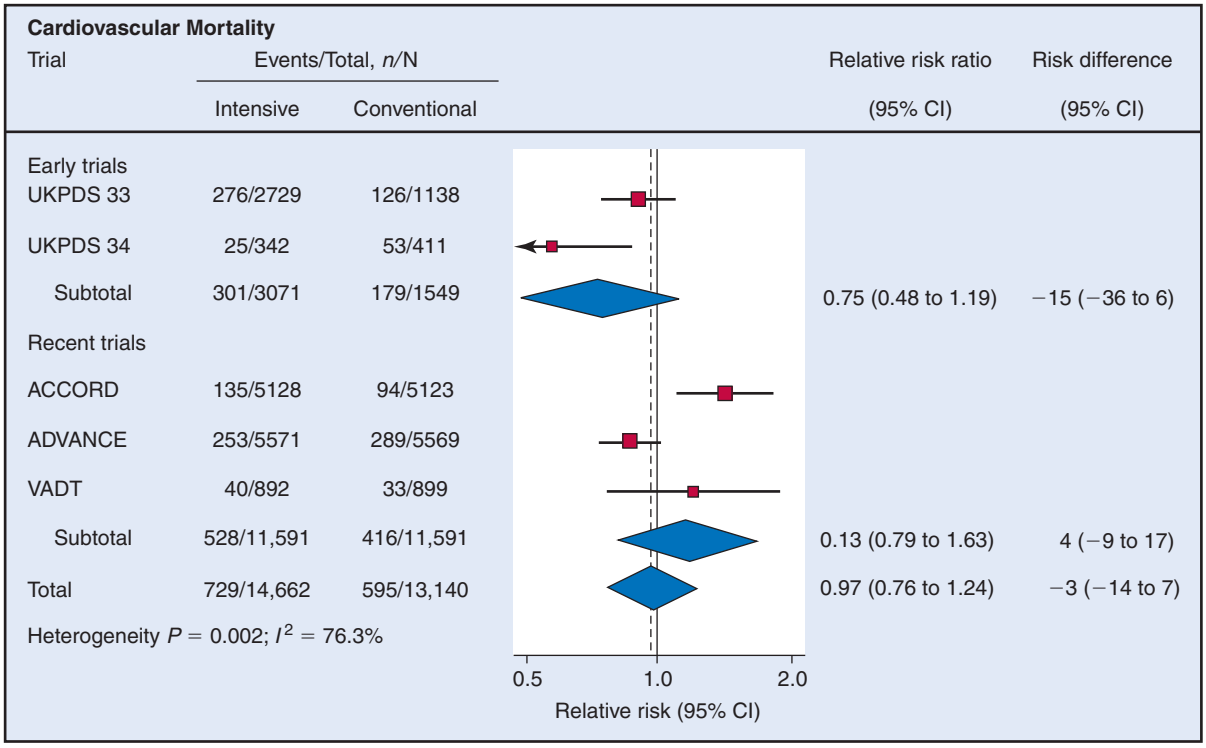
TRIALS OF GLUCOSE-LOWERING INTERVENTIONS IN PREDIABETES AND EARLY DIABETES

Because one potential reason for the lack of benefit of intensive glucose lowering on cardiovascular disease is that it is applied too late to prevent atherosclerosis, it is worthwhile to examine studies that have investigated glucose lowering before diabetes actually develops or very early in the disease course.

One such study was the Diabetes Prevention Program that randomly assigned 3234 nondiabetic persons at high risk for diabetes (with elevated body mass index and fasting and postload glucose values) to intensive lifestyle therapy, metformin monotherapy, or placebo.[29] Lifestyle intervention and metformin both significantly reduced the incidence of subsequent diabetes. In follow-up studies of the trial population, the lifestyle intervention also improved cardiovascular risk factors compared with metformin or placebo treatment, but the number of cardiovascular events was too small



A



B

FIGURE 13-4 **Relative risk and risk differences estimates (per 1000 patients over 5 years of treatment), with 95% confidence intervals (CI), for the main study outcomes in the UKPDS, ACCORD, ADVANCE, and VADT. A,** Primary composite cardiovascular outcome. **B,** Cardiovascular mortality. *(Modified from Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes,* Ann Intern Med *151:394-403, 2009.)*

(n = 89 at 3 years) to allow any meaningful examination of the differences among groups.[30] After 10 years of follow-up of the Diabetes Prevention Program, the cumulative incidence of diabetes was still lowest in the former lifestyle intervention group.[31] Cardiovascular disease risk factors improved in all three treatment groups, but averaged over all follow-up, systolic and diastolic blood pressure and triglyceride levels were lower in the lifestyle than in the other groups (even though the use of antihypertensive medications was less frequent). However, the number of clinical events remained too small to determine the effect of diabetes prevention strategies on actual cardiovascular events.



In the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), investigators examined the effect of postprandial glucose lowering on the incidence of diabetes in 1429 participants with impaired glucose tolerance, elevated fasting glucose, and overweight or obesity.[32] As a secondary outcome, investigators specifically examined the effect of intervention on major cardiovascular events and hypertension, although the trial was not adequately powered to answer that question. The participants were randomized to receive either acarbose or placebo and were followed for a mean of 3.3 years. In the course of the trial, almost one quarter of participants discontinued participation prematurely (including significantly greater numbers randomized to acarbose). Moreover, concerns about inconsistencies, failure to follow intention-to-treat analysis, and changes in the trial endpoints have been raised. Nevertheless, the trial reported an unanticipated 49% relative risk reduction ($P=0.03$) in major cardiovascular events (including revascularization procedures, congestive heart failure, and peripheral vascular disease in addition to the conventional major cardiovascular events) associated with acarbose therapy. This composite endpoint was primarily driven by an incredible 91% reduction in MI ($P=0.02$). Clearly, these trial findings will need to be confirmed in future studies before acarbose therapy can be recommended for cardiovascular risk reduction. One such trial, the Acarbose Cardiovascular Evaluation (ACE) study, is currently ongoing and testing the impact of acarbose on cardiovascular outcomes in persons with impaired glucose tolerance and established cardiovascular disease or acute coronary syndromes.

Encouraged by the STOP-NIDDM results, investigators of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial decided to test an alternative postprandial glucose-lowering approach with a short-acting insulin secretagogue, nateglinide, in addition to lifestyle modification. They randomized 9306 persons (mean age 64) with impaired glucose tolerance (baseline HbA1c 5.8%) at high risk for cardiovascular disease (24% had a prior history of cardiovascular events) to nateglinide or placebo and followed participants for a median of 5 years. Nateglinide did not reduce the occurrence of the three co-primary outcomes—incident diabetes (HR 1.07, $P=0.05$), cardiovascular outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure, HR 0.94, $P=0.43$), or the extended cardiovascular outcome (which in addition included unstable angina or arterial revascularization, HR 0.93, $P=0.16$). The trial results contrast sharply with the findings of the STOP-NIDDM study and show that targeting postprandial hyperglycemia with nateglinide in participants with impaired glucose tolerance does not lead to cardiovascular benefits.

Another potential approach is to test whether early provision of basal insulin to normalize fasting plasma glucose may reduce cardiovascular outcomes in persons with mildly elevated glucose levels or early diabetes. This strategy does not specifically target postprandial hyperglycemia, but rather postulates that insulin, which has been demonstrated to have anti-inflammatory effects, may actually be cardioprotective and that it may also preserve pancreatic beta cell function over time. The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial randomized 12,537 people (mean age 64; 82% with early diabetes, 6% with new diabetes, and 12% with impaired fasting glucose or impaired glucose tolerance; median baseline HbA1c 6.4%; 59% with prior cardiovascular disease) to insulin glargine or standard care.[33] The target in the insulin group was to achieve a fasting glucose level of 95 mg/dL or lower. After a median 6 years of follow-up, HbA1c levels were 6.2% versus 6.5% in the insulin and standard arms, respectively. The trial found no significant reduction in two co-primary outcomes, major cardiovascular events (HR 1.02, $P=0.63$) and major cardiovascular events plus revascularization and heart failure (HR 1.04, $P=0.27$). However, there was an increased risk of hypoglycemia with insulin therapy and some weight gain (+1.6 kg versus −0.5 kg in the two groups). Although diabetes incidence was decreased (a finding of questionable clinical application), the trial findings were generally disappointing. The ORIGIN trial did not support the original hypothesis that normalizing glucose with early insulin therapy would lead to better cardiovascular outcomes.

These studies illustrate the impact of glucose lowering with a variety of different approaches in persons with prediabetes or early diabetes on cardiovascular outcomes. With the exception of the STOP-NIDDM study, which had important limitations, the studies to date have not supported the notion that glucose lowering is beneficial for cardiovascular outcomes at the prediabetic stage. Despite the epidemiologic association of glucose with cardiovascular events that extends well into the nondiabetic range, interventions targeting glycemia have thus far failed to deliver an effective strategy to reduce this risk.

THE "HOW" OF GLUCOSE LOWERING: THE EVIDENCE FOR SPECIFIC MEDICATIONS AND MEDICATION CLASSES

Perhaps one of the most important lessons in cardiovascular risk reduction in type 2 diabetes has been the growing recognition that the exact strategy used to reduce glucose may actually matter with respect to outcomes. For several decades now, the thrust of clinical research has been to test approaches that target specific degrees of glucose lowering. Less attention was previously paid to the different ways in which glycemia is actually improved and how that may affect downstream events. The early UKPDS experience, albeit based on a small subgroup (n = 342) of patients, has given metformin a preferred place in the diabetic regimen for type 2 diabetes. In most subsequent trials (ACCORD, ADVANCE, VADT), combinations of various medications, including insulin use, had to be used to lower glucose levels, and there was no particular advantage to one strategy versus another. However, these glucose-lowering trials were not designed to test the effects of specific medications on outcomes.

Interest in the effects of specific antihyperglycemic medications on outcomes was boosted by the publication of a meta-analysis by Nissen and colleagues in 2007 that showed an adverse effect of the thiazolidinedione rosiglitazone on MI risk.[34] In the analysis of 42 trials that was performed, there were 86 MI events in the rosiglitazone group compared with 71 in the comparator arm (including placebo, metformin, sulfonylurea, or insulin), resulting in an increased odds ratio of 1.43 ($P=0.03$). Although the methodology and the results of this meta-analysis have been debated, and some have noted no increase in risk associated with rosiglitazone use,[35,36] there is no doubt that the study provided a

cautionary tale for glucose lowering. Most important, the study suggested that even though a medication may reduce glucose levels, and thus appear to treat diabetes effectively, it may in fact increase the risk of clinical events that are the target of glucose lowering in the first place. After the rosiglitazone experience, however, the U.S. Food and Drug Administration (FDA) mandated that glucose-lowering medications must have data that support their safety with respect to cardiovascular events before they are approved for use in diabetes.[37]

Despite the intense interest in the specific effects of medication classes (and individual agents) that followed, there is a paucity of data to guide choice of therapy in diabetes with respect to long-term outcomes. Indeed, a recent comparative effectiveness analysis of 140 trials and 26 observational studies of medications for type 2 diabetes concluded that evidence on long-term clinical outcomes, including mortality, cardiovascular disease, nephropathy, and neuropathy, was of low strength and insufficient.[38] Evidence supported metformin as a first-line agent in treatment of diabetes, but this evidence was primarily based on its efficacy to lower HbA1c levels, safety, adverse effect profile, and cost. We shall now review the available evidence for the major classes of antihyperglycemic therapy. These results are summarized in **Table 13-1**.

Metformin

Metformin, which works primarily by reducing hepatic glucose production, remains the first-line agent in the treatment of type 2 diabetes because it effectively reduces HbA1c levels, is weight-neutral, and does not lead to hypoglycemia when used as monotherapy. It is also inexpensive, has a favorable safety profile, and may have potential benefit with respect to cardiovascular disease, based on the UKPDS substudy.[16]

Despite the many advantages of metformin, data with respect to cardiovascular risk reduction with metformin are not entirely consistent. In addition to the UKPDS substudy,[16] only one prior randomized controlled trial was conducted on this subject. In the trial, 390 patients treated with insulin were randomized to receive either metformin or placebo as add-on therapy.[39] The primary endpoint, an aggregate of microvascular and macrovascular outcomes, did not differ between the two groups after 4.3 years of follow-up (HR 0.92, $P=0.33$), but there was a significant reduction in the secondary endpoint of macrovascular events (HR 0.60, $P=0.04$). In addition, metformin use was associated with beneficial effects on body weight and insulin requirements.

In observational studies, metformin use (either as monotherapy or in combination with another oral agent) has been associated with reduced mortality,[40–42] cardiovascular deaths,[40] and cardiovascular events.[41–43] Because metformin is generally the preferred initial agent for diabetes treatment and remains contraindicated in patients with advanced chronic kidney disease, patients who are not treated with this medication in an observational study may differ in important ways from those who are. These analyses either adjusted for potential confounders or matched patient populations for the propensity to be prescribed metformin versus another medication (usually a sulfonylurea). However, these investigations were observational in nature, so unmeasured factors may potentially still have contributed to the differences in outcomes.

Alongside the evidence that supports the safety and effectiveness of metformin, there are data that provide a less reassuring picture. Although the UKPDS substudy showed benefits of metformin in overweight participants, the trial also reported an increased death rate in nonoverweight patients who took metformin and a sulfonylurea compared with those who took a sulfonylurea alone (relative risk 1.60, $P=0.04$).[16] Combined analysis of the two UKPDS studies did not reveal an increased risk for mortality in patients treated with this combination, and the increased mortality in the UKPDS substudy has not been fully explained. In a subsequent meta-analysis of 13 randomized controlled trials involving more than 13,000 type 2 diabetes patients, compared with other treatments, metformin therapy had no significant effect on the risk for mortality (relative risk 0.99 with wide 95% confidence intervals that could not exclude a 25%

TABLE 13-1 Major Randomized Controlled Trials in Type 2 Diabetes

	UKPDS	ACCORD	ADVANCE	VADT
Study Participants				
Mean age, years	53	62	66	60
Diabetes duration, years	New	10	8	11.5
Prior macrovascular disease	Excluded*	35%	32%	40%
Duration of Study				
Number of years	11	3.5	5	5.6
HbA1c Goal				
Intensive therapy	†	<6%	≤6.5%	<6%
Standard therapy	‡	7%-7.9%	Standard	8%-9%
HbA1c Achieved				
Intensive therapy	7.0%	6.4%	6.4%	6.9%
Standard therapy	7.9%	7.5%	7.0%	8.5%
Severe Hypoglycemia				
Annual events per 100 patients	0.71	4.6	0.56	12.0
Intensive therapy	0.20	1.5	0.30	4.0
Standard therapy	Not reported	<0.001	<0.001	<0.001
P value				
Primary Outcome§				
HR (95% CI) for intensive versus standard therapy	**0.88 (0.79-0.99)**	0.90 (0.78-1.04)	0.90 (0.82-0.98)	0.88 (0.74-1.05)
All-Cause Mortality				
HR (95% CI) for intensive versus standard therapy	0.94 (0.80-1.10)	**1.22 (1.01-1.46)**	0.93 (0.83-1.06)	1.07 (0.81-1.42)
Cardiovascular Mortality				
HR (95% CI) for intensive versus standard therapy	0.94 (0.66-1.30)	**1.35 (1.04-1.76)**	0.88 (0.74-1.04)	1.32 (0.81-2.14)

HR=Hazard ratio; CI=confidence interval
Bolded results represent HR reaching statistical significance, $P<0.05$.
*Excluded myocardial infarction (MI) within 1 year prior, heart failure, angina, or more than one vascular event.
†Based on fasting plasma glucose (FPG) <108 mg/dL.
‡Based on FPG <270 mg/dL.
§An aggregate endpoint of any diabetes-related endpoint (UKPDS); a composite of nonfatal myocardial infarction, nonfatal stroke, and fatal myocardial infarction and stroke (ACCORD); combined microvascular and macrovascular disease (ADVANCE); and time to occurrence of a composite of major cardiovascular events (VADT).
(Data from Ismail-Beigi F, Moghissi E, Tiktin M, et al. Individualizing glycemic targets in type 2 diabetes mellitus: Implications of recent clinical trials, *Ann Intern Med* 154:554–559, 2011.)

reduction or 31% increase in risk), cardiovascular mortality (relative risk 1.05), or rates of MI (relative risk 0.90 with 95% confidence intervals that could not exclude 26% risk reduction or 9% harm).[23] Similar findings were reported in a meta-analysis that specifically examined the effects of metformin with insulin compared with insulin alone in 23 trials with over 2000 participants.[44] The study found that metformin added to insulin did not significantly change mortality risk (relative risk 1.30, with 95% confidence intervals 0.57 to 2.99) or cardiovascular mortality risk (relative risk 1.70, with 95% confidence intervals 0.35 to 8.30) but provided little reassurance with regard to each of these endpoints given the wide confidence intervals.

Sulfonylureas

Sulfonylureas, insulin secretagogues, are the oldest oral agent class for treatment of hyperglycemia. Whereas sulfonylureas are effective at glucose lowering, they increase the risk of hypoglycemia, are associated with a modest weight gain, and likely result in less durable effects on glucose control compared with metformin or thiazolidinediones.[45]

Questions about cardiovascular safety of sulfonylureas date back to 1970 when the University Group Diabetes Program (UGDP) trial reported an increased risk for cardiovascular death associated with the use of tolbutamide compared with placebo or insulin.[46] Subsequently the FDA mandated a boxed warning for all sulfonylureas. Sulfonylureas inhibit the adenosine triphosphate (ATP)–dependent potassium channels that are present within cardiomyocytes and coronary vascular endothelial cells, and it has been postulated that the presence of sulfonylureas at the time of an acute coronary event prevents adequate coronary vasodilation and thus may result in a larger area of myocardial damage. However, the risk of cardiovascular death noted by the UGDP group was not supported by the subsequent UKPDS study, which showed no difference in cardiovascular risk between the use of sulfonylureas (chlorpropamide, glibenclamide, or glipizide) or insulin therapy[15] (but a benefit with the use of metformin, as noted earlier[16]). The large A Diabetes Outcome Prevention Trial (ADOPT) study compared metformin, rosiglitazone, or glyburide therapy with respect to glycemic control, but again found no difference with respect to cardiovascular events (which were not frequent and were collected as adverse events during the trial) across the treatment groups after 4 years of treatment.[45] Finally, the ADVANCE study of intensive glucose lowering primarily used gliclazide in its intensive glucose control arm and found no risk associated with this strategy.[22]

Subsequent observational studies have, however, mostly suggested harm with sulfonylurea treatment, especially compared with metformin therapy.[40,41,47,48] Whether sulfonylureas are associated with adverse effects or metformin is protective remains debatable. Sulfonylureas are still considered a viable option for second-line therapy in diabetes, primarily based on their effectiveness in lowering glucose and extensive accrued experience with the use of these agents.

Thiazolidinediones

Thiazolidinediones, which lower glucose by activating the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ), are insulin sensitizers. They do not increase the risk of hypoglycemia and may result in more durable blood glucose control than sulfonylureas or metformin.[45] Although these agents improve many intermediate markers of cardiovascular risk (e.g., C-reactive protein and markers of endothelial function), they are associated with substantial weight gain, lower-extremity edema, heart failure, bone fractures, and possibly bladder cancer risk.

Rosiglitazone, but not pioglitazone, has actually been associated with an increased risk of MI,[34] which led to its restricted use in diabetes. Therefore the two members of the thiazolidinediones class need to be considered separately if their individual risks and benefits are to be understood. It is worth noting that most analyses of the effects of glucose-lowering therapies on clinical outcomes group together medications of the same class and perform class-based comparisons. This practice is based on the assumption that medications in the same class have a similar mode of action and therefore will have a similar effect on clinical outcomes. The experience with rosiglitazone and pioglitazone, both members of the thiazolidinedione class, suggest that individual medications within the same class can affect clinical outcomes in different ways.

As already mentioned, the effect of rosiglitazone on cardiovascular events was analyzed in a highly publicized meta-analysis, which showed an increased risk of MI associated with its use.[34] Several other meta-analyses confirmed adverse effects associated with rosiglitazone,[49,50] but not all found harm.[35,36] However, observational studies comparing rosiglitazone with other oral diabetes medications[51] or with pioglitazone[52–54] have consistently shown increased risk of mortality and heart failure with rosiglitazone use. The only trial specifically designed to evaluate cardiovascular outcomes associated with rosiglitazone was the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study.[55] RECORD randomized 4447 diabetes patients with inadequately controlled hyperglycemia treated with metformin or sulfonylurea monotherapy to receive, in addition, a sulfonylurea, metformin, or rosiglitazone. In the final analysis of the trial, there was no difference in the primary endpoint (cardiovascular hospitalization or cardiovascular death) among the groups, but the event rate was lower than expected and the dropout rate in the trial was high, decreasing the power to detect significant differences in outcomes. Notably, the risk of heart failure was increased approximately twofold with rosiglitazone.

Finally, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 2368 patients with type 2 diabetes and obstructive coronary artery disease were factorially randomized to a) medical therapy with insulin provision [insulin or sulfonylurea] versus insulin sensitization [metformin or rosiglitazone]); and b) randomized to medical treatment versus coronary revascularization (a priori determined to be percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), evaluating the effects on death and major cardiovascular events.[56] There was no difference in the rates of death and cardiovascular events between patients undergoing revascularization or medical therapy, or between strategies of insulin provision and insulin sensitization. However, in the CABG stratum, risk of major cardiovascular events was significantly lower with revascularization and insulin sensitization (18.7%) compared with insulin sensitization therapy alone (32%, $P=0.002$).

Because rosiglitazone was the primary thiazolidinedione used for insulin sensitization, there did not appear to be harm associated with its use in the setting of this trial. However, the trial was not designed to specifically address rosiglitazone's safety.

Given the weight of the evidence, in 2011 the FDA placed restrictions on prescription and use of rosiglitazone-containing medications through a Risk Evaluation and Mitigation Strategy (REMS).[57] The use of rosiglitazone was limited to patients already successfully treated with this medication, or patients whose blood glucose levels could not be controlled with other antihyperglycemia medicines and who did not wish to use pioglitazone instead. In June 2013, the FDA reviewed readjudicated data from the RECORD trial and concluded that the trial had not found an elevated risk of MI or death associated with rosiglitazone. Therefore in November 2013 the FDA lifted its earlier restrictions on rosiglitazone use. Given the highly publicized debates over the safety of rosiglitazone, it is unclear if this medication will ever become widely used again in patients with type 2 diabetes.

In contrast to rosiglitazone, data with pioglitazone appear to be more reassuring with respect to cardiovascular outcomes.[48,52–54,58] The largest completed trial investigating effects of pioglitazone on cardiovascular outcomes was the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, in which 5238 patients with type 2 diabetes and established macrovascular disease received pioglitazone or placebo, added to their baseline diabetes therapy.[59] After an average follow up of 2.9 years, there was a 10% relative risk reduction in the primary endpoint (including all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, revascularization, and above-knee amputation), but this did not reach statistical significance ($P=0.095$) (**Fig. 13-5**). The secondary, and more conventional, outcome of major cardiovascular events was significantly decreased with pioglitazone (HR 0.84, $P=0.03$). Concerns have been raised about the late definition of the secondary endpoint after the trial was under way, the large number of secondary endpoints (more than eight), and the increased risk of heart failure in the intervention group (16% versus 11.5%), which may have, over time, negatively affected study results.

In summary, the cardiovascular benefits of thiazolidinediones are not entirely clear. The association of rosiglitazone with MI, heart failure, and mortality is concerning, and most guidelines recommend against the use of rosiglitazone for those reasons. The potential benefits of pioglitazone in the PROactive study must be weighed against the increased risk of heart failure and fractures.

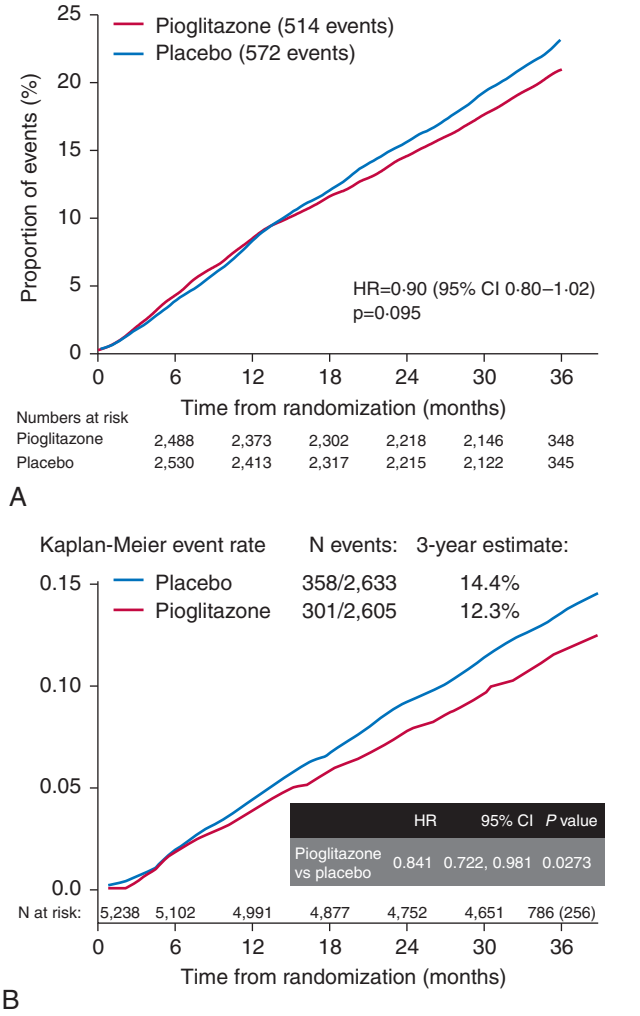


FIGURE 13-5 PROactive study. Time to primary composite endpoint (all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, revascularization, and above-knee amputation) and time to secondary endpoint (major cardiovascular events).

Insulin

As type 2 diabetes progresses, beta cell function declines and the effectiveness of oral agents for glucose control diminishes. However, endogenous insulin secretion is not entirely lost in type 2 diabetes, and strategies for insulin use can be less complex than those used in the treatment of type 1 diabetes. The main side effects of insulin use are weight gain and hypoglycemia. Given that insulin has been used in clinical practice for decades and is a naturally occurring peptide hormone, fewer concerns have been previously raised about its cardiovascular safety. However, insulin may obviously induce hypoglycemia, which may in turn promote adrenergic discharges and arrhythmia, promotes fluid retention, and may result in hypokalemia (especially when administered intravenously) as a result of potassium shifts from the extracellular to intracellular space. Recent concerns about the cardiovascular safety of insulin use in type 2 diabetes have been raised.[60] These concerns are primarily based on observational studies that show an increased risk of mortality, cardiovascular mortality, and cardiovascular events in diabetes patients treated with insulin compared with other agents.[12,61–63] In one such recent analysis, data on over 84,000 patients with type 2 diabetes in the GPRD were used to determine the risk of the primary outcome (first major adverse cardiac event, first cancer, or mortality) associated with five different glucose-lowering regimens (metformin monotherapy, sulfonylurea monotherapy, insulin monotherapy, metformin plus sulfonylurea, and insulin plus metformin).[63] When compared with all other regimens, insulin monotherapy was associated with an increased risk of the primary outcome and all-cause mortality. The observational nature of the study does not permit conclusions about the causal nature of these associations; the risk of harms may be mediated by insulin itself or by the clinical characteristics of patients who require and are prescribed insulin. Indeed, there were important differences in baseline characteristics



among treatment groups; despite adjustment for a variety of variables, residual confounding remains an important limitation.

Although few trials have specifically focused on the effectiveness and safety of insulin for prevention of cardiovascular events, several trials have tested the use of insulin during and after an acute MI for secondary prevention of cardiovascular disease and mortality. The first Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed significant reduction in mortality (absolute reduction of 11%) associated with the use of insulin-glucose infusion during admission and subcutaneous insulin after hospitalization for glycemic control compared with standard therapy in diabetic patients.[64] Because it was unclear whether the mortality benefit was the result of inpatient or outpatient glycemic control in DIGAMI, the DIGAMI-2 study tested three different strategies, including combinations of insulin-based inpatient and outpatient glycemic control regimens.[65] However, the study struggled with patient recruitment and did not achieve differences in glycemic control among the three groups. There were no differences in mortality among the three groups. However, in the post hoc analysis of the DIGAMI-2 trial, insulin treatment was actually associated with an increased risk for nonfatal cardiovascular events, but not mortality.[66]

The previously described ORIGIN trial provided more reassuring evidence on the use of insulin glargine in adults with prediabetes or early diabetes but did not suggest cardiovascular benefits.[33] The use of insulin in this trial was associated with a very modest reduction in already low HbA1c levels (6.3% versus 6.0% in the standard versus insulin group, respectively) at the end of 2 years, no significant reduction in the cardiovascular endpoints, but increase in weight gain and hypoglycemic events. Moreover, there was no effect of glargine on the incidence of various cancers, a concern raised because of insulin's role in cell growth, differentiation, and proliferation and because of epidemiologic studies pointing to the increased risk of cancer associated with its use.[67,68]

Incretin-Based Therapies

Medications that work through the incretin system have been relatively recently introduced into the type 2 diabetes pharmacopeia. These agents either mimic or increase the circulating concentrations of endogenous glucagon-like peptide 1 (GLP-1), thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying, and decreasing appetite. The main advantage of the injectable GLP-1 agonists is weight loss, which is modest in most patients but can be significant in some. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. Concerns regarding an increased risk of pancreatitis remain unresolved. The oral dipeptidyl peptidase 4 (DPP-4) inhibitors work predominately through effects on the endocrine pancreas and appear to be weight neutral. Typically, neither of the incretin-based classes causes hypoglycemia as monotherapy.

Give the recent introduction of these agents to the market and limited long-term experience, results of trials evaluating cardiovascular outcomes are only beginning to be reported, and many are still under way (**Table 13-2**). GLP-1 analogues are effective in improving glycemic control and reduce several cardiovascular risk factors. Based on animal studies, GLP-1–based therapy may mitigate ischemia-induced cardiac injury,[69] but more data will be needed to assess long-term cardiovascular outcomes in humans.[70]

More information is currently available on the cardiovascular effects of DPP-4 inhibitors, and so far they appear to neither increase nor decrease cardiovascular events.[71,72] These effects are disappointing, given that several industry-sponsored pooled cardiovascular analyses of DPP-4 inhibitors described risk ratios well below 1 for cardiovascular events,[73–75] raising hopes for a class of agents that could actually reduce cardiovascular risk. However, two large randomized controlled trials showed that saxagliptin and alogliptin had an overall neutral effect on major cardiovascular events. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, 16,492 patients with type 2 diabetes who had risk factors or a history of cardiovascular events were assigned to receive saxagliptin or placebo in addition to their existing diabetes medication therapy.[71] After a median of 2.1 years, there was no difference in the primary endpoint (MI, ischemic stroke, or cardiovascular death) between the two groups (HR 1.0, 95% CI 0.89-1.12). However, more patients in the saxagliptin group reported hypoglycemic events (15.3% versus 11.7%, $P<0.001$), and, somewhat unexpectedly, more patients on saxagliptin were hospitalized for heart failure (3.5% versus 2.8%, $P=0.007$). The findings of increased heart failure risk are concerning and warrant additional investigation. In the Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care (EXAMINE) trial, 5380 patients with type 2 diabetes who had had an acute coronary event in the preceding 15 to 90 days were randomly assigned to receive either alogliptin or placebo in addition to an existing antihyperglycemic regimen.[72] Similar to the findings of the SAVOR trial, there was no difference in the primary endpoint (MI, stroke, or cardiovascular death) between the two groups (HR 0.96, upper boundary of the one-sided CI 1.16). Heart failure hospitalization was not a prespecified endpoint in EXAMINE, but when it was examined in a post hoc fashion (including those events that occurred after a primary endpoint), there were numerically, but not statistically, more events in the alogliptin group (106 versus 89, HR 1.19, $P=0.22$).[76] Three other DPP-4 inhibitor cardiovascular trials are currently ongoing (TECOS [saxagliptin], CAROLINA [linagliptin] and CARMELINA (linagliptin)). Several others involving GLP-1 receptor agonists (LEADER [liraglutide], EXSCEL [exenatide once weekly exenatide], ELIXA (lixisenatide), SUSTAIN 6 [semaglutide]) will provide additional data needed to assess cardiovascular effects of these therapies.[69]

In summary, incretin-based therapies reduce HbA1c levels, do not lead to hypoglycemia (at least, as monotherapy), and are not associated with weight gain or MI, stroke, or cardiovascular death. Therefore they appear to be attractive agents for the management of type 2 diabetes. On the other hand, they are very expensive, they may increase the risk of heart failure in the case of saxagliptin, and their other long-term risks and benefits are not yet known.

Other Agents

Acarbose is an alpha-glucosidase inhibitor that delays gut carbohydrate absorption. Acarbose is infrequently used in

TABLE 13-2 Summary of Cardiovascular Effects Associated with Various Classes of Glucose-Lowering Agents

AGENT	MECHANISM OF ACTION	EXPECTED HBA1C REDUCTION	ADVERSE EFFECTS	CARDIOVASCULAR EFFECTS
Sulfonylureas				
Glyburide (aka glibenclamide) Glipizide Glimepiride Gliclazide Tolbutamide Chlorpropamide	Bind to sulfonylurea receptors on pancreatic islet cells, closing K_{ATP} channels, stimulating insulin release. Relatively long duration of action.	Approximately 1%-2%	Hypoglycemia Weight gain	Hypoglycemia may precipitate ischemia, arrhythmia. Cardiac K_{ATP} channel closure may impair ischemic preconditioning. Observational studies suggest worse CVD outcomes compared with metformin.
Glinides				
Repaglinide Nateglinide	Bind to sulfonylurea receptors on pancreatic islet cells, closing K_{ATP} channels, stimulating insulin release. Relatively short duration of action.	Approximately 1%-2%	Hypoglycemia Weight gain	Hypoglycemia may precipitate ischemia, arrhythmia. Cardiac K_{ATP} channel closure may impair ischemic preconditioning. Few CVD outcome studies exist.
Biguanide				
Metformin	Activates AMP-kinase and reduces hepatic glucose production.	Approximately 1%-2%	Diarrhea, nausea Lactic acidosis Decreases B_{12} levels	May improve CVD outcomes (UKPDS 34). Favorable CVD outcomes in most observational studies. Should not be used in patients with acute or unstable HF because of lactic acidosis risk.
α-Glucosidase Inhibitors				
Voglibose Acarbose Miglitol	Slow gut carbohydrate absorption.	Approximately 0.5%-1.0%	Gas, bloating	May reduce MI risk (STOP-NIDDM).
Thiazolidinediones				
Pioglitazone Rosiglitazone	Activate the nuclear receptor PPAR-γ, increasing peripheral insulin sensitivity. Also reduce hepatic glucose production.	Approximately 1%-1.5%	Weight gain Edema, HF Fractures ? Bladder cancer (pioglitazone)	Contraindicated in NYHA Class III or IV HF (because of fluid retention); not recommended in Class II HF. Pioglitazone may reduce MI, stroke risk (PROactive) but increases HF risk. Rosiglitazone may increase MI risk.
GLP-1 Receptor Agonists				
Exenatide Liraglutide Albiglutide	Increase glucose-dependent insulin secretion, decrease glucagon secretion, and delay gastric emptying.	Approximately 1%-1.5% Approximately 0.6%-0.8%	Nausea, vomiting —	Long-term outcomes not known.
DPP-4 Inhibitors				
Sitagliptin Saxagliptin Linagliptin Vildagliptin Alogliptin	Inhibit degradation of endogenous GLP-1 (and GIP-1), thereby enhancing incretin levels.			Alogliptin and saxagliptin have a neutral effect on cardiovascular outcomes, but saxagliptin may increase risk of HF.
Amylin Analogue				
Pramlintide	Decreases glucagon secretion and delays gastric emptying.	Approximately 0.4%-0.6%	Nausea, vomiting	Long-term outcomes not known.
Insulins				
Glargine, detemir, degludec NPH Regular Lispro, aspart, glulisine Premixed	Increase insulin supply.	Theoretically limitless	Hypoglycemia Weight gain Edema (at high doses)	Few randomized controlled trials show neutral effects on cardiovascular outcomes, but observational studies suggest increased risk of cardiovascular events and mortality compared with oral antihyperglycemic agents.
SGLT-2 Inhibitors				
Canagliflozin Dapagliflozin Empagliflozin	Blocks reabsorption of filtered glucose load in the proximal tubule, leading to glucosuria	Approximately 0.5%-1.0%	Genital mycotic infections Urinary tract infections Reversible decrease in GFR Hemodynamic side effects Increase in LDL-cholesterol	Reduction in systolic blood pressure Weight loss No long-term data on CV outcomes

AMP = Adenosine monophosphate; CVD = Cardiovascular disease; GFR = glomerular filtration rate; GIP-1 = Gastric inhibitory polypeptide-1; GLP-1 = Glucagon-like peptide-1; HF = Heart failure; K_{ATP} = adenosine triphosphate (ATP) sensitive potassium channel; NYHA = New York Heart Association; SGLT-2 = sodium-glucose co-transporter 2.
Data from Inzucchi and McGuire.

the United States because of gastrointestinal side effects. Post hoc analyses of the STOP-NIDDM trial showed a reduction in cardiovascular endpoints, but, as mentioned earlier, there were problems with the trial design and conduct.[32] Another agent, colesevelam, a bile acid sequestrant, is typically used to lower low-density lipoprotein (LDL) levels, but also modestly reduces glucose. The dopamine agonist bromocriptine reduces glucose levels, but very modestly, and is available in the United States only for antihyperglycemic therapy. A 52-week trial evaluated the short-term overall and cardiovascular safety of bromocriptine in type 2 diabetes.[77] The frequency of serious adverse events was comparable between treatment arms, but fewer patients experienced cardiovascular events in the bromocriptine compared with the placebo group (HR 0.60, 95% CI 0.35-0.96). Future studies will need to confirm whether bromocriptine is indeed associated with cardiovascular risk reduction in the long-term.

Newer agents, such as the SGLT-2 inhibitors, that lower glucose by inhibiting a renal cotransporter and thereby decrease glucose reabsorption in the kidney, have been recently approved by the FDA, but studies are under way to determine their long-term safety and efficacy.[78,79] Short-term studies suggest that these agents lower HbA1c by 0.5% to 1%, do not lead to hypoglycemia (in monotherapy), and lower blood pressure and weight, but are associated with mycotic genital infections and adverse events related to osmotic diuresis.[80–85] Other glucose-lowering medications that stimulate glucose-dependent insulin secretion are being tested for their efficacy and safety, as well.[86] It will take some time to understand the cardiovascular impact of these newer agents on patients with type 2 diabetes.

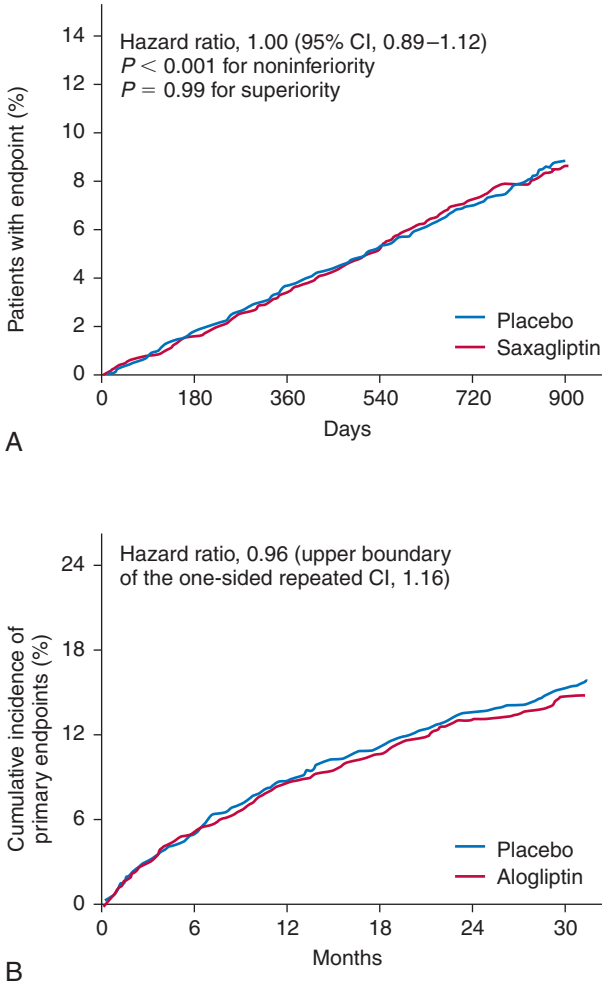


FIGURE 13-6 Summary of results from **A,** SAVOR and **B,** EXAMINE trials, in which saxagliptin and alogliptin were compared against placebo with respect to major cardiovascular outcomes (myocardial infarction, stroke, or cardiovascular death).[71] *(Modified from NEJM.)*

RISKS ASSOCIATED WITH ANTIHYPERGLYCEMIC MEDICATIONS

If efforts to reduce glucose levels were not associated with any risk, there might be less hesitation to normalize them in diabetic patients. In reality, the benefits of glucose lowering must be weighed against the burden of treatment and known, as well as potential, risks of therapy. Because data on the impact of various anti-hyperglycemic agents on long-term clinical outcomes are limited, clinical decisions about the type and intensity of glucose lowering must be made with some uncertainty in mind (**Fig. 13-6**). We will now review data on the known risks associated with antihyperglycemic agents. This information is critical to informed decision making and should be discussed with patients as strategies for treatment are considered.

Hypoglycemia

The pursuit of strict glucose control is frequently hampered by concerns over hypoglycemia. Hypoglycemia requiring third-party assistance is common in the course of type 2 diabetes therapy and occurs with a frequency of approximately 35 episodes per 100 patient-years among insulin-treated patients.[87] Hypoglycemia occurring during treatment has been associated with several adverse events, including increased mortality,[88,89] higher risk of dementia,[90] falls,[91] fall-related fractures,[92] cardiovascular events,[89,93,94] and poor health-related quality of life.[95,96]

In particular, the relationship between hypoglycemia and subsequent cardiac events warrants attention. There are a number of plausible mechanisms by which acute hypoglycemia may trigger ischemia, arrhythmia, and cardiovascular events (**Fig. 13-7**). Hypoglycemia increases the levels of counterregulatory hormones, such as epinephrine and norepinephrine, which may induce increased cardiac rate and/or contractility, heightening myocardial oxygen consumption, while also precipitating vasoconstriction and platelet aggregation. Acute hypoglycemia in the presence of hypokalemia prolongs cardiac repolarization, increases the QT interval, favoring a proarrhythmic state. One study of type 1 and type 2 diabetic patients who presented to the hospital with severe hypoglycemia documented frequent hypokalemia, QT prolongation, and severe hypertension during the hypoglycemic events.[97] Although animal studies have verified the effect of hypoglycemia on myocardial ischemic injury,[98] the data in humans are less clear, and debates continue on whether hypoglycemia is a mediator or merely a marker of such adverse outcomes—that is, does the propensity toward hypoglycemia simply identify sicker individuals who have lost the ability to counterregulate?

Clinical trial data consistently show that assignment to an intensive glucose control strategy is associated with a two-fold to threefold higher risk of hypoglycemia compared with standard care.[15,18,22,99,100] In trial settings, hypoglycemia requiring third-party assistance occurred with a frequency

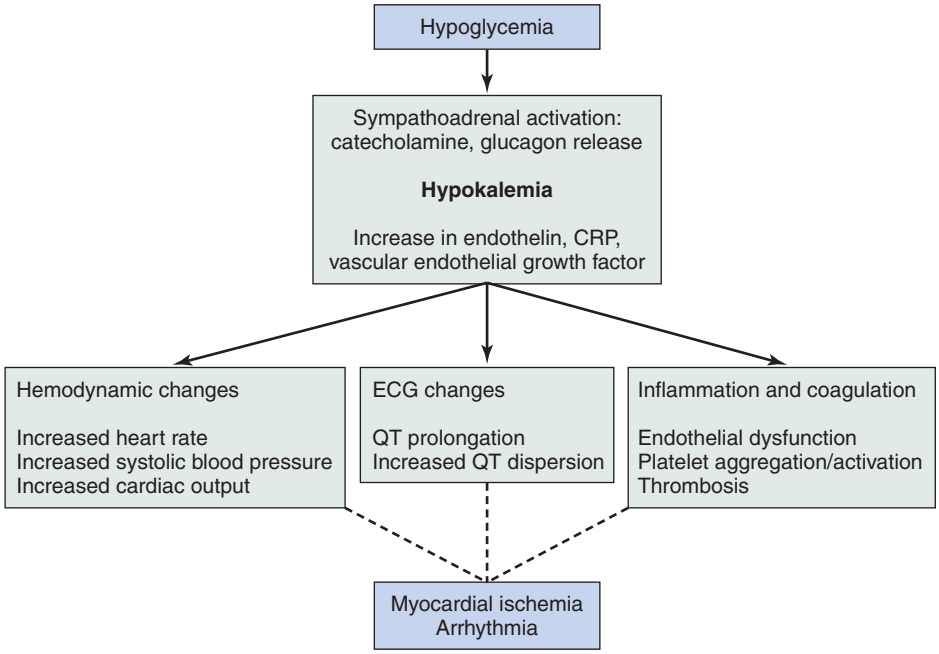


FIGURE 13-7 Proposed mechanisms linking hypoglycemia with cardiovascular events. CRP = C-reactive protein; EKG = Electrocardiogram.

of 0.6 to 12 events annually per 100 patients in the intensive therapy group and 0.2 to 4 events in the standard therapy group—much less frequently than in the community setting. Although the relationship between intensive therapy and hypoglycemia appears clear, the relationship between achieved level of glycemic control and hypoglycemia is more complex. In the Diabetes Control and Complications Trial (DCCT) of type 1 diabetes patients, an inverse relationship between HbA1c level and serious hypoglycemia was noted, with the number of events logically increasing with decreasing HbA1c.[100] In contrast, however, detailed post hoc analyses of ACCORD participants with type 2 diabetes showed that patients with poorer glycemic control had a higher risk of hypoglycemia, irrespective of treatment assignment.[101] In fact, a greater drop in HbA1c level during the first 4 months of the trial was not associated with increased hypoglycemia risk. Rather, patients who started out with higher baseline HbA1c levels and were unable to reduce their blood glucose levels appeared to be at the highest risk for this complication. Moreover, participants with persistently elevated HbA1c levels above 7% after initiation of the intensive strategy had a higher mortality risk than those achieving lower glycemic levels (<7%).[19] What is actually mediating the higher risk of hypoglycemia and mortality in this setting is unclear, but the findings suggest that aggressive attempts to intensify treatment in patients who remain hyperglycemic may confer a very high risk for subsequent hypoglycemia.

Other apparent risk factors for hypoglycemia, aside from intensive glucose lowering, include treatment with insulin or sulfonylurea medications,[102] older age,[101] lower health literacy level,[103] longer duration of diabetes,[101] renal impairment,[102] polypharmacy,[104] baseline cognitive impairment,[105] and recent admission to the hospital within 30 days.[104]

Other Adverse Effects of Medications

Intensive glucose control usually requires polypharmacy to achieve HbA1c targets, and adverse effects of medications require careful consideration. Even in patients who do not choose tight glycemic targets, multiple medications to lower glucose are often required with increasing duration of the disease, as beta cell function declines.

The relative importance of various adverse effects of medications may vary from patient to patient. Weight gain is typically associated with the use of insulin, sulfonylureas, and thiazolidinediones. Heart failure, edema, and fractures are associated with the use of thiazolidinediones. Gastrointestinal side effects complicate treatment with metformin, acarbose, and some of the incretin-based therapies. In general, drug reactions increase in frequency with the use of multiple medications. Addition of another medication to lower glucose may also pose a financial burden and significantly increase time and effort required to manage diabetes (including, potentially, capillary blood glucose monitoring).

IMPLICATIONS FOR CLINICAL PRACTICE

What is the effect of glucose management on CHD events in patients with type 2 diabetes? Based on the available data, intensive glucose lowering appears, at best, to modestly decrease the risk of CHD by approximately 15% when compared with standard glucose strategies. Assuming a 10-year risk of CHD of 17.4% (control arm of UKPDS), the number needed to treat (NNT) ranges on the order of 41 to 46 over 10 years to prevent one CHD event.[106] What about type of antihyperglycemic therapy? Our understanding of the implications of the specific type of therapy on these outcomes is only beginning to emerge. Best cardiovascular outcomes appear to be associated with the use of metformin, but these data are based only on a small subgroup of UKPDS patients and observational data. Sulfonylureas compared with metformin appear to be associated with inferior results, and the impact of thiazolidinediones remains somewhat unclear (with a suggestion of better outcomes for CHD with pioglitazone, but an increase in heart failure). The effect of newer incretin-based therapies on cardiovascular outcomes appears neutral so far.

Who is the patient, and what are his or her goals for care? To help patients make the best decisions about their care, clinicians must consider the clinical characteristics of a patient and the context in which he or she lives to determine how these various factors may influence the relationship between treatment and outcomes. Data to guide this type of individualized treatment are lacking, and future research is critically needed to provide better information to guide personalized decisions. Based on existing data, patients with high levels of comorbidity may derive less cardiovascular benefit from intensive glucose control,[107] and most guidelines suggest higher glycemic targets for older patients with longer duration of diabetes, established cardiovascular disease, and high risk of hypoglycemia. Naturally, these patients are at higher underlying risk of CHD, but they appear to benefit less from tight glycemic control. In contrast, the benefits of aggressive lipid and blood pressure control appear to be greatest based on high underlying CHD risk, although the relative benefits will clearly depend also on competing mortality risk and current medications.[107]

As already suggested, central to the decision making about treatment are patient's preferences and goals for care. Patient-centered care needs to begin by eliciting these preferences and goals, because understanding them is indispensable for providing care that is responsive to and respectful of patients' needs. A shared decision-making process stresses a partnership between the patient's values and preferences and the physician's knowledge of clinical evidence and judgment. Decisions are highly individualized, based on available evidence, and uncertainty must be acknowledged when it exists. As an example, more intensive glycemic control in a patient already struggling with a complex regimen may lead to an overburdened patient who is unable to cope with his or her disease. Indeed, somewhat paradoxically, pushing forward with intensive antihyperglycemic therapy may decrease adherence to other more evidence-based therapies. In such a circumstance, it may be reasonable to liberalize glycemic targets to some degree. On the other hand, a patient whose most important goal is prevention of diabetes complications may choose to take on the additional burden of insulin therapy or multiple medications to control blood glucose levels with high intensity.

How to prioritize glucose lowering within the patient's overall diabetes care plan is also critically important. Clearly, statin therapy, smoking cessation, aspirin for appropriate patients, and blood pressure control are the central pillars of cardiovascular risk reduction. On a population level, based on UKPDS data, fewer persons would need to be treated with tight blood pressure control (NNT 23) than intensive glucose control (NNT 46) to prevent one MI event.[108] Similarly, lipid therapy for primary prevention (NNT 34 or 35) and secondary prevention (NNT 13 or 14) appears to be more effective for cardiovascular events than intensive glucose control.[109] However, for individual patients, the optimal strategy is still unknown. It is also unclear whether patients will do better if each problem is addressed sequentially or if they are addressed simultaneously, and how this varies based on degree of out-of-range risk factor levels.

Despite decades of study, we remain largely ignorant of the benefits and risks of antihyperglycemic therapy as it relates to cardiovascular disease risk. Research in the coming decade needs to provide us with better information so that patients can make decisions about glucose targets and antihyperglycemic strategies that optimize their outcomes.

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14 Effect of Blood Pressure Management on Coronary Heart Disease Risk in Patients with Type 2 Diabetes



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The effects of aggressive blood pressure (BP) management on the risks of coronary heart disease (CHD) and other vascular outcomes among individuals with type 2 diabetes mellitus (T2DM) has been a matter of intense debate recently, with the results of large-scale clinical trials leading to variable interpretation. This chapter reviews the epidemiologic associations between BP and CHD in diabetes and the efficacy of BP lowering on CHD outcomes, focusing on evidence about the direct and off-target effects of different classes of BP-lowering drugs, the results of relevant clinical trials evaluating the relative merits of intensive BP management, and the potential role of new and emerging clinical interventions. Finally, these will be placed within the context of effects of BP lowering on other clinical outcomes, the role of absolute risk assessment for guiding BP management, and a global perspective of current levels of success in achieving adequate BP control in patients with T2DM.

EPIDEMIOLOGIC ASSOCIATIONS BETWEEN BLOOD PRESSURE AND CORONARY HEART DISEASE IN PEOPLE WITH TYPE 2 DIABETES MELLITUS

On average, systolic BP (SBP) and diastolic BP (DBP) are consistently higher among individuals with T2DM compared with those without T2DM.[1,2] Nonoptimal BP is a well-established risk factor for people with and without diabetes. In general populations, there is clear log-linear association between both SBP and DBP and CHD, evident within any adult age group. This association appears continuous across the range of BP, down to at least SBP of 115 mm Hg and DBP of 75 mm Hg, such that for adults aged 40 to 89 years, a 20-mm Hg difference in SBP is associated with an approximate 45% difference in risk of CHD.[3] In 386,307 people with diabetes included in the Asia Pacific Cohort Studies Collaboration,[4] a similar continuous association was observed for both Asian and non-Asian populations. Among those with diabetes, a 10-mm Hg lower level of SBP was associated with an 18% lower level of CHD, which was not statistically different from the 23% lower level of CHD observed in people without diabetes (**Fig. 14-1**).

Further data relating to epidemiologic associations have been derived from observational analyses of clinical trial populations.[5,6] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a higher level of average SBP within a range from below 120 mm Hg to above 160 mm Hg was associated with a greater risk of myocardial infarction (MI) of approximately 12%/10-mm Hg increment.[6] More recently, observational subgroup analyses of the International Verapamil SR Trandolapril Study (INVEST) suggested a possible J-curve relationship with a threshold on-treatment SBP level of 125 to 130 mm Hg in diabetic patients with established stable coronary artery disease with respect to all-cause mortality.[7] By and large, however, the epidemiologic data have formed a credible basis for the hypothesis that benefits of BP-lowering therapy might accrue to individuals with T2DM down to levels of SBP well below currently accepted thresholds for the diagnosis of hypertension.

Although these epidemiologic data provide a basis for expecting a reduction in CHD events from interventions that reduce BP in people with T2DM, the results from well-designed and appropriately powered randomized trials should inform recommendations for clinical and public health practice. Such trials have been conducted, evaluating both lifestyle interventions and drugs, and are summarized in the following sections.

EFFICACY OF LIFESTYLE INTERVENTIONS ON BLOOD PRESSURE LEVELS AND CORONARY HEART DISEASE RISK IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Initial attempts at BP reduction through lifestyle modification are emphasized in guidelines for the management of hypertension worldwide in individuals with or without diabetes.[8–13] These have principally focused on increasing physical activity, reducing body weight and/or adiposity,

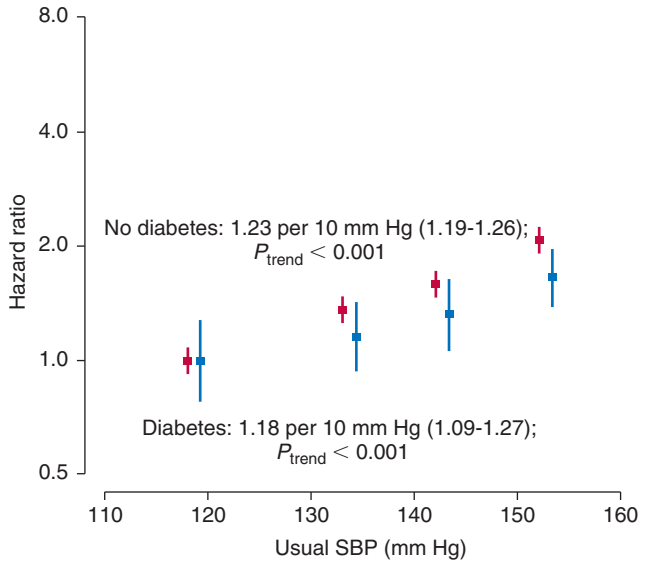


FIGURE 14-1 Association between usual systolic blood pressure (SBP) and coronary heart disease (CHD) events by diabetes status in the Asia Pacific Cohort Studies Collaboration. For each association, the hazard ratio (95% confidence interval [CI]) for a 10-mm Hg higher level of systolic blood pressure (SBP) compared with SBP 120 mm Hg as reference and the *P* value for linear trend are indicated (upper value for those without diabetes *[red]*; lower value for those with diabetes *[blue]*). Usual = baseline values corrected for regression dilution bias (using repeated measures). *(Reproduced with permission from Asia Pacific Cohort Studies Collaboration; Kengne AP, Patel A, Barzi F, et al: Systolic blood pressure, diabetes and the risk of cardiovascular diseases in the Asia-Pacific region,* J Hypertens *25:1205-1213, 2007.)*

and performing dietary modification, including salt restriction. Although a number of studies have evaluated the effects of lifestyle interventions on diabetes incidence, the Look AHEAD (Action for Health in Diabetes) trial examined the sustained effects of an intensive lifestyle intervention in 5145 overweight or obese adults with T2DM.[14] Over an average of 4 years and compared with a diabetes support and education control group, intensive lifestyle intervention was associated with significant improvements for a number of vascular risk factors, including significant net reductions in SBP (−2.33 mm Hg) and DBP (−0.44 mm Hg). The intervention evaluated and targeted both physical activity and diet, and separate effects of individual components of the lifestyle intervention on BP cannot be estimated. Inferences about how this might translate to reductions in CHD risk currently can be based only on projections from observational studies comparing BP level or changes in BP level with clinical outcomes. Published data from Look AHEAD to date are the result of a prespecified interim comparison of effects on risk factors only, in a trial designed to evaluate the effects of the intensive lifestyle intervention on clinical outcomes after an average of 13.5 years of follow-up. (See also **Chapters 5** and **12**.)

Although not restricted to people with diabetes, the Dietary Approaches to Stop Hypertension (DASH) trials provide some indication of the likely effects of certain diets on BP.[15,16] Allocation to the DASH diet (rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat) in 459 adults over an 8-week intervention period was associated with significant reductions in SBP and DBP of 5.5 mm Hg and 3.0 mm Hg, respectively, compared with a "typical" control diet.[15] In the subsequent DASH-sodium trial,[16] participants were randomly assigned different levels of sodium intake, within DASH or control diets. The effects of different levels of sodium intake in addition to the DASH diet were evaluated. Greatest benefits were observed with a low-sodium DASH diet, which compared with a control high-sodium diet, reduced SBP by 11.5 mm Hg in participants with hypertension and 7.1 mm Hg in those without a diagnosis of hypertension. With small numbers of participants, analysis in the subgroup with diabetes was not possible. A recent updated Cochrane Review of 167 studies concluded that dietary sodium reduction over at least 4 weeks resulted in significant reductions in BP, with greater effects among people with hypertension versus those considered normotensive and possibly in non-Caucasians versus Caucasians.[17] Although there are some dissenting views, many believe the existing evidence adequately favors common recommendations for individual salt intake to be limited to less than 5 g/day, particularly in individuals with hypertension,[18] although a Cochrane review of individual patient strategies to reduce salt intake suggest that more effective approaches to achieve such reductions are urgently required.[19]

EFFICACY AND SAFETY OF BLOOD PRESSURE–LOWERING DRUGS ON CORONARY HEART DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Multiple guidelines for pharmacologic lowering of BP in patients with T2DM exist worldwide, with some major examples summarized in **Table 14-1**. Some of the evidence on which these recommendations are based is outlined here.

Overall Efficacy—Placebo-Controlled Trials

The most comprehensive overview of the effects of BP-lowering medications on vascular outcomes is provided by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC). There have been two cycles of prospectively defined group and individual participant data meta-analyses conducted through this collaboration, most recently in 2003.[20] The systematic reviews of placebo-controlled trials in the second cycle included nine studies and 25,731 individuals. The researchers concluded that, compared with placebo, angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists each reduced the risk of CHD by approximately 20% in general populations, with much greater precision around the estimate for ACE inhibitors. Further analyses of placebo-controlled comparisons among individuals with and without diabetes did not find any evidence of statistical heterogeneity for effects on CHD (**Fig. 14-2**).[21]

Since the second cycle of the BPLTTC was published, the largest-ever-conducted placebo-controlled trial of BP lowering among individuals with T2DM was completed. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial was a randomized study of 11,140 individuals with T2DM from 214 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America.[22,23] Participants with known cardiovascular or microvascular disease or with at least one major risk factor for cardiovascular disease and any initial level of BP and glycosylated hemoglobin were randomly assigned, in a factorial design, to a fixed combination of the ACE inhibitor perindopril and the thiazide diuretic indapamide (4/1.25 mg) or matching placebo,

TABLE 14-1 Summary of Select Major Guideline Recommendations for the Use of BP-Lowering Drugs in Patients with T2DM

GUIDELINE	PRINCIPLES FOR COMMENCING BP-LOWERING TREATMENT	RECOMMENDED CLASSES OF BP-LOWERING DRUG	RECOMMENDED TARGET BP LEVELS
Global: International Diabetes Federation Global Guideline for Type 2 Diabetes, 2012 (www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf)	Consider BP-lowering treatment if BP is consistently above 130/80 mm Hg. All people with known cardiovascular disease should receive BP-lowering therapy unless contraindicated or not tolerated.	In the absence of a raised urinary albumin excretion rate, any agent can be used as first-line therapy except for alpha-adrenergic blockers. ACE inhibitors and ARBs may offer some advantages over other agents in some situations, but the two should not be used together. CCBs should be avoided in heart failure. Use beta-adrenergic blockers in people with angina; beta-adrenergic blockers and ACE inhibitors in people with coronary artery disease; ACE inhibitors or diuretics in those with heart failure; ACE inhibitor plus low-dose thiazide or thiazide-like diuretic, or ACE-inhibitor plus CCB in people with cerebrovascular disease. Care should be taken with combined thiazide and β-adrenergic blockers because of risk of deterioration in metabolic control. Add further medications from a different class if targets are not reached on maximal doses of current medications.	Aim to maintain BP ≤130/80 mm Hg, if therapy is well tolerated. Revise individual targets upward if there is significant risk of postural hypotension and falls. Higher targets should be used in older adults.
United States: American Diabetes Association Clinical Practice Recommendations, 2013 (http://care.diabetesjournals.org/content/36/Supplement_1)	Patients with confirmed BP ≥140/80 mm Hg should have prompt initiation and timely subsequent titration of pharmacologic therapy.	Commence with a regimen that includes either an ACE inhibitor or an ARB; if one class is not tolerated, substitute the other. Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve BP targets.	People with diabetes and hypertension should be treated to a SBP goal of <140 mm Hg. Lower SBP targets, such as <130 mm Hg, may be appropriate for certain individuals, such as younger patients. Patients with diabetes should be treated to a DBP <80 mm Hg.
United States: Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), 2003* (www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf)	Patients not at goal BP (<130/80 mm Hg) after attempts at lifestyle modification should be commenced on drug treatment.	Regarding the selection of medications, clinical trials with diuretics, ACE inhibitors, BBs, ARBs, and calcium antagonists have a demonstrated benefit in the treatment of hypertension in type 2 diabetes. The question of which class of agent is superior for lowering BP is somewhat moot because most diabetic patients will require two or more drugs to achieve BP control.	BP in patients with diabetes should be controlled to levels of 130/80 mm Hg or lower.
Europe: European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension, 2013 (www.escardio.org/guidelines-surveys/esc-guidelines/Pages/arterial-hypertension.aspx)	Although initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mm Hg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mm Hg.	All classes of antihypertensive agents are recommended and can be used in patients with diabetes. RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. It is recommended that individual drug choice take comorbidities into account. Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.	An SBP goal <140 mm Hg is recommended in patients with diabetes. The DBP target in patients with diabetes is recommended to be <85 mm Hg.

*Release of JNC 8 is expected during 2013.
ACE = Angiotensin converting enzyme; ARB = angiotensin receptor blocker; BB = beta blockers; CCB = calcium channel blocker; RAS = renin angiotensin system.

and to intensive glucose control or standard guideline-based glucose control. The two primary outcomes were a composite of major cardiovascular (nonfatal acute MI, nonfatal stroke and cardiovascular death) and major microvascular events (new or worsening nephropathy and microvascular eye disease), analyzed jointly and separately. The average duration of follow-up was 4.3 years for the BP-lowering intervention. It is important to note that in the BP treatment comparison aspect of the study, ADVANCE was testing the effects of a strategy of routinely administering BP-lowering therapy to individuals with diabetes at high risk for a cardiovascular event, regardless of initial BP level. Specifically, this trial was not designed to evaluate different target BP levels.

The mean BP of participants at study baseline in ADVANCE was 145/81 mm Hg, with over 40% recording a BP below the conventional threshold of hypertension of 140/90 mm Hg. Over the course of active treatment, BP was reduced by a mean of 5.6/2.2 mm Hg compared with placebo. At the end of follow-up, the mean BP achieved was 134.7/74.8 mm Hg in the perindopril-indapamide group

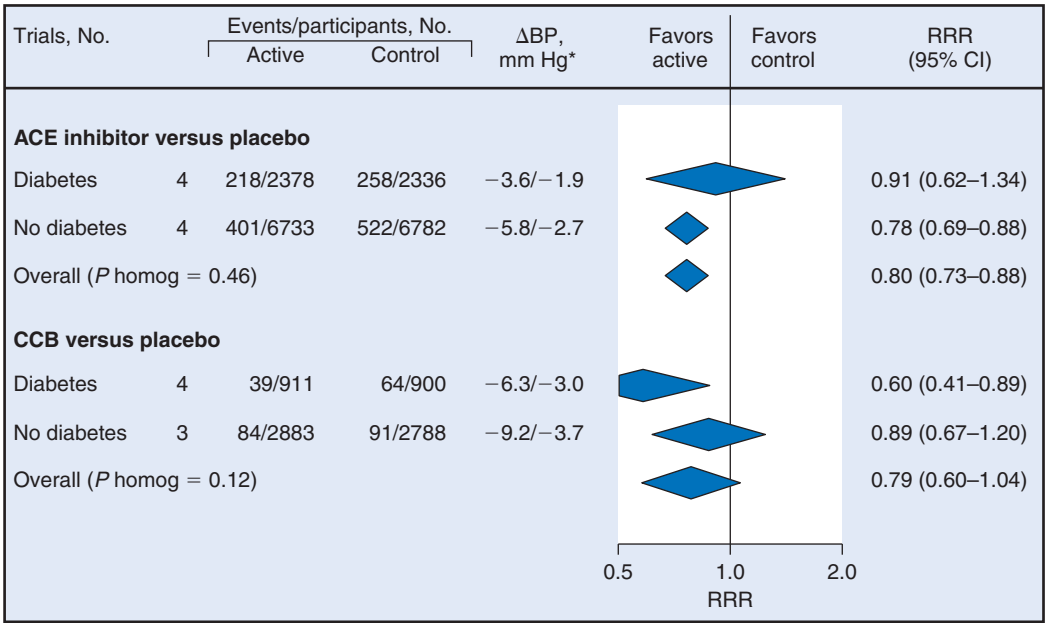


FIGURE 14-2 Effects of BP-lowering medication classes versus placebo on the risk of CHD in patients with and without diabetes mellitus. Asterisk indicates the overall mean BP difference (systolic and diastolic) during follow-up in the actively treated or first-listed group compared with the control or second-listed group, calculated by weighting the difference observed in each contributing trial by the number of individuals in the trial. Negative values indicate lower mean follow-up BP levels in first-listed treatment groups than in second-listed groups. ACE = Angiotensin converting enzyme; CCB = calcium channel blocker; CI = confidence interval; RRR = relative risk ratio. *(Modified from Turnbull F, Neal B, Algert C, et al: Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials,* Arch Intern Med *165:1410-1419, 2005.)*

and 140.3/77.0 mm Hg in the placebo group. Active treatment reduced the risk of the combined composite primary outcome of major microvascular and macrovascular (cardiovascular) events by 9% (95% confidence interval [CI] 0% to 17%, $P = 0.043$). Considered individually, the effect on major macrovascular events was of similar magnitude but not statistically significant between the randomized groups. Among those on active treatment, there was a 14% (2%-25%; $P = 0.025$) reduction in all-cause mortality, driven by an 18% (2%-32%; $P = 0.027$) reduction in cardiovascular mortality. In addition, there was a 14% (2%-24%; $P = 0.020$) relative risk reduction in CHD events (defined as death caused by CHD, nonfatal MI, silent MI, coronary revascularization, or hospital admission for unstable angina), all of which were prespecified secondary outcomes. There was no evidence of heterogeneity in treatment effect in subgroups of participants defined by key baseline characteristics including age, sex history of cardiovascular disease, and background use of BP-lowering therapy. In particular, the effects of the combination perindopril and indapamide treatment were similar across a range of initial BP levels and regardless of use of other concomitant preventive therapies (including other BP-lowering agents, statins, and aspirin). The results of this BP intervention aspect of the ADVANCE study point to the potential benefits of an alternative strategy for delivery of BP-lowering treatment, as opposed to traditional threshold and target-driven strategies in which therapy is limited to patients with arbitrarily defined "hypertension" and therefore potentially denied to a broader range of high-risk individuals with apparently "normal" BP levels.

Comparative Efficacy of Blood Pressure–Lowering Drugs

There has been considerable debate about the potential existence of BP-independent beneficial effects of various classes of drugs used to lower BP in a broad group of high-risk patients, including those with diabetes and with respect to different vascular beds. This possibility of differential class effects was explored extensively in the second cycle of BPLTTC, which analyzed data from 29 trials, specifically focused on the magnitude of benefits on clinical outcomes produced by different regimens of BP-lowering therapy, and attempted to relate any observed differences to effects on BP through meta-regression.[20] In general populations and based on head-to-head comparisons, there were no significant differences among regimens based on ACE inhibitors, calcium channel blockers diuretics, or beta blockers. Overall, the efficacy of treatment correlated well with the degree of BP reduction achieved, although separate meta-regression has suggested modest additional BP lowering–independent effects of ACE inhibitors on CHD risk.[24] This question has also been explored through comparisons of individuals with and without diabetes, using data from 29 randomized trials (33,395 individuals with diabetes and 125,314 participants without diabetes).[21] Comparisons among individuals with diabetes showed point estimates favoring ACE inhibitors versus either diuretics or beta blockers, or versus calcium channel blockers for the prevention of CHD events; however, these were not statistically significant. There was no evidence of differential effects on CHD outcomes when calcium channel blockers were compared with diuretics or beta blockers. For all outcomes, there was no clear evidence of heterogeneity in the estimates of comparative treatment effects on CHD between individuals with and without diabetes (**Fig. 14-3**).

Although not limited to patients with diabetes, the results of three trials published after the second cycle of BPLTTC provide some evidence about the potential merits of different BP-lowering regimens in diabetic patients. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) investigated people with hypertension and additional risk factors for cardiovascular disease, and compared the effects of

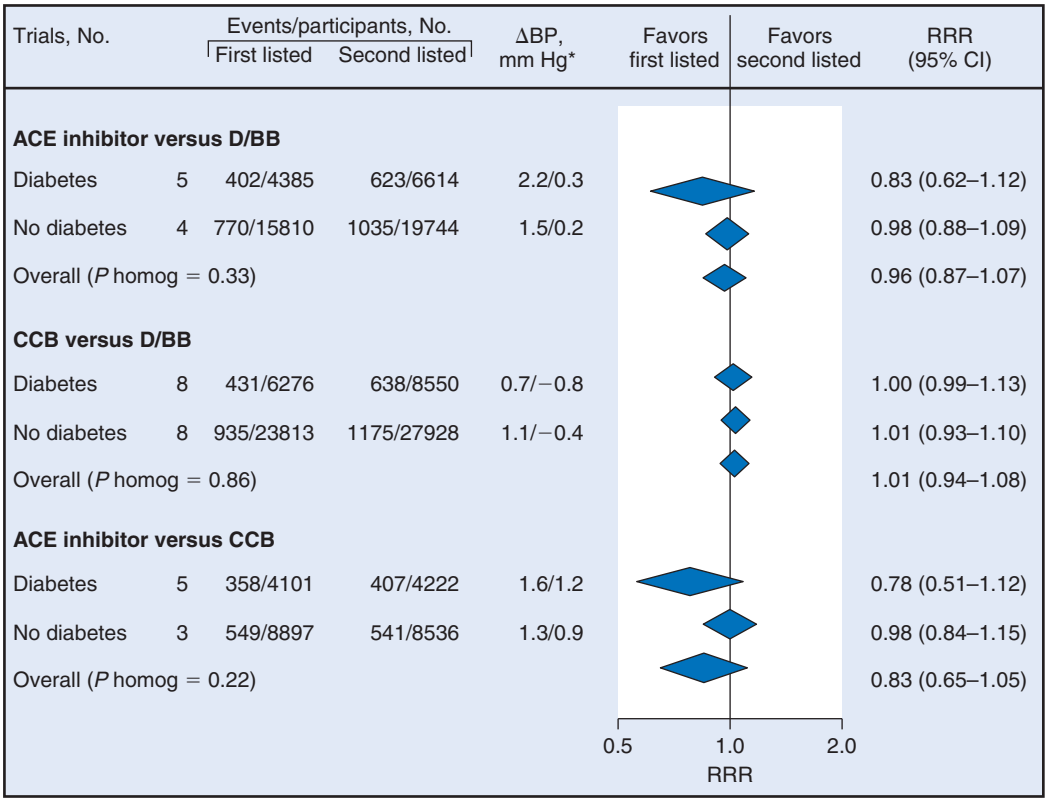


FIGURE 14-3 Effects of BP-lowering regimens based on different medication classes on the risk of CHD in patients with and without diabetes mellitus. Conventions as per Figure 14-2. D/BB = Diuretic/beta blocker *(Modified from Turnbull F, Neal B, Algert C, et al: Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials,* Arch Intern Med *165:1410-1419, 2005.)*

combinations of atenolol with a thiazide diuretic versus amlodipine with perindopril on the primary outcome of fatal and nonfatal CHD events.[25] The trial involved 19,257 participants, 27% of whom had diabetes at study entry. The point estimate of treatment effect favored the amlodipine-perindopril combination for the primary outcome, but this was not statistically significant. However, there were significant reductions in all secondary outcomes associated with the amlodipine-perindopril combination, ranging from a relative risk reduction of 11% to 24%, and including all-cause mortality (which led to early termination of the trial), all coronary events, and non-fatal MI and fatal CHD. However, it should be noted that despite a goal of achieving similar BP levels in both treatment arms, the amlodipine-based regimen was associated with a significant 2.7/1.9 mm Hg lower BP over the duration of follow-up. There was no evidence of heterogeneity of the treatment effect by the presence or absence of diabetes, evaluated on the basis of total cardiovascular outcomes.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) included 25,620 patients at increased risk for cardiovascular disease.[26] Approximately 40% of study participants had diabetes at study entry. Patients were randomized to ramipril alone, to telmisartan alone, or to both drugs. The mean BP level at study entry was 142/82 mm Hg. Over the course of follow-up, BP was 2.4/1.4 mm Hg lower in the combination therapy group compared with the ramipril-alone group. The incidence of the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalized heart failure) did not differ between the ramipril-alone group and each of the other randomized groups. As expected, participants allocated to telmisartan alone experienced less cough and angioedema than those who were randomized to ramipril. However, symptoms of hypotension occurred more frequently in the telmisartan group (2.7%) and in the combination group (4.8%) compared with the ramipril-alone group (1.7%). Renal dysfunction was observed most often in the combination group. It is important to note that there was no heterogeneity in treatment effects by diabetes status for the primary outcome. In summary, the results of ONTARGET confirmed comparable efficacy of the ACE inhibitor and the ARB, but provided no evidence of additional benefit from combination therapy.

The Avoiding Cardiovascular Events through Combination Therapy to Patients Living with Systolic Hypertension (ACCOMPLISH) trial is also relevant to populations with diabetes.[27] Approximately 60% of the 11,506 high-risk patients with hypertension included in this study had an additional diagnosis of diabetes at study entry. Participants were randomly allocated to receive one of two combination drug regimens—the ACE inhibitor benazepril plus the calcium channel blocker amlodipine, or benazepril with the diuretic hydrochlorothiazide (HCT). The mean baseline BP level was 145/80 mm Hg. Over the duration of follow-up, a 0.9/1.1-mm Hg lower BP was observed in the benazepril-amlodipine group compared with the benazepril-HCT group. This study was stopped prematurely after a mean follow-up period of 3 years because of an observed statistically significant 20% reduction in the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after cardiac arrest, and coronary revascularization) in the benazepril-amlodipine group compared with the benazepril-HCT group. As with ONTARGET, there was no

evidence of heterogeneity based on baseline diagnosis of diabetes. Although early concerns had been expressed about potential underestimation of the BP difference between treatment arms using on-trial measurements, subsequent results of 24-hour ambulatory BP monitoring in a subset of 573 participants did not show any significant differences.[28]

By and large, current hypertension and diabetes management guidelines worldwide acknowledge that achieving BP reduction is more pressing than decisions about which class of drug should be used, particularly given that two or more agents are frequently required in patients with diabetes.[8–13] In general, use of a regimen that includes an ACE-inhibitor or an angiotensin receptor blocker (ARB) is recommended, particularly in the presence of albuminuria. Although thiazide or thiazide-like diuretics as well as beta blockers have been associated with adverse effects on glucose homeostasis, the clinical relevance of this is doubtful and it does not preclude the use of these drugs in people with T2DM. Indeed, the indications for use of beta blockers in patients with existing CHD or systolic heart failure (particularly vasodilating beta blockers, such as carvedilol and nebivolol, which may also have more favorable metabolic effects than older beta blockers[29,30]) and thiazide or thiazide-like diuretics in those with cerebrovascular disease are compelling.[31,32] For much of the world, affordability of different classes of BP-lowering drugs is also a key issue that must be considered in choice of antihypertensive therapy.

More versus Less Blood Pressure Lowering and Target Blood Pressure Levels

Although acknowledging limitations of available randomized evidence, most guidelines worldwide currently recommend more aggressive management of hypertension (mostly, a target of 130/80 mm Hg or lower) among people with diabetes compared with those without diabetes.[8–13] In 1998, the UKPDS was the landmark trial that first compared more intensive BP lowering (with an ACE inhibitor or a beta blocker–based regimen) with less intensive control among newly diagnosed patients with T2DM and hypertension. The target BP levels for the randomized groups were below 150/85 mm Hg versus below 180/105 mm Hg, respectively. Achieved mean final BP levels were 144/82 mm Hg in the more intensive BP-lowering arm and 154/87 mm Hg in the less intensive BP-lowering arm. Compared with less tight control, more intensive BP lowering resulted in significant reductions in all "diabetes-related endpoints," as well as cerebrovascular events and microvascular disease.[33] For the secondary outcome of MI (fatal or nonfatal MI or sudden death), however, the observed relative risk reduction was not statistically significant (21% [95% CI −7% to 41%]). The second cycle of BPLTTC also addressed the question of whether more versus less BP reduction confers additional advantages, and for the outcome of CHD alone, the result was inconclusive.[20] However, the weighted mean BP differences among randomized groups within each trial appeared to correlate well with the magnitude of reduction of CHD risk (**Fig. 14-4**). Furthermore, there was no evidence of statistical heterogeneity between those with and without diabetes.[21]

Before the most recent evidence provided by the ADVANCE trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Mancia and Grassi summarized the effects of BP-lowering drugs in patients with diabetes, focusing on entry and on-treatment BP levels

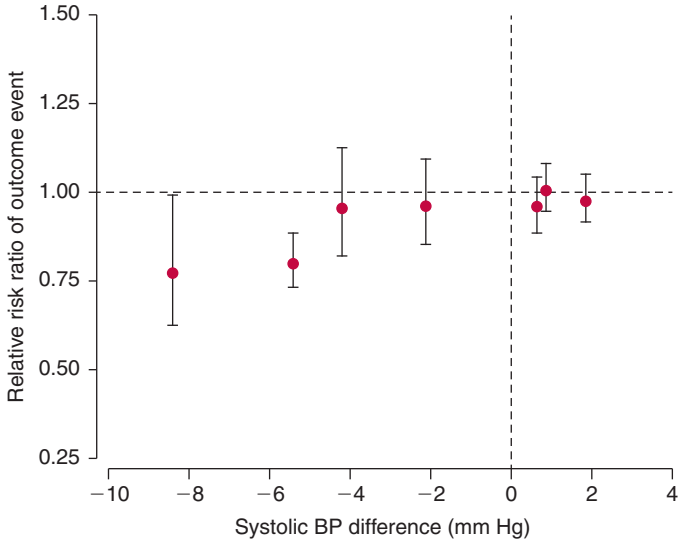


FIGURE 14-4 Associations of BP differences between groups with risks of CHD in seven published randomized trials comparing more versus less intensive blood pressure control. The circles are plotted at the point estimate of effect for the relative risk for every event type and the mean follow-up BP among randomized groups. *(From Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials,* Lancet *362:1527-1535, 2003.)*

(**Fig. 14-5**). As can be seen, few data existed in relation to achieved SBP levels below 135 mm Hg, despite prevailing guideline recommendations.

The ACCORD trial was specifically designed to address a question of appropriate target BP levels in people with T2DM. This was a factorially randomized trial of 10,251 individuals with T2DM from 77 centers in North America.[34–36] Participants with a hemoglobin A1c (HbA1c) of 7.5% or more and aged 40 years or older with cardiovascular disease or 55 years or older with anatomic evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity) were randomized to intensive glucose control (aiming for HbA1c levels $\leq$6.0%) or standard control (aiming for HbA1c levels of 7.0% to 7.9%) (see also **Chapter 13**). Subsets of participants were also included in a factorially randomized evaluation of a BP-lowering intervention (n = 4733) or a lipid management intervention (n = 5518). The objective of the BP-lowering component of the study was to specifically examine the effects of targeting different SBP levels (an SBP target of 120 mm Hg or less, compared with 140 mm Hg or less). Participants who had SBP between 130 and 180 mm Hg on three or fewer antihypertensive medications and with no evidence of greater than 1.0 g of proteinuria per day or the equivalent were included. The BP-lowering regimen was at the physician's discretion but included any class of drug therapy known to produce cardiovascular benefits (ACE inhibitors, ARBs, diuretics, calcium channel blockers, or beta blockers). The primary outcome was a composite of major cardiovascular events defined as nonfatal MI, nonfatal stroke, and cardiovascular death. Secondary outcomes included all coronary events, all stroke events, and all-cause death, considered separately.

The mean baseline BP in ACCORD was 139/76 mm Hg, and at study entry, 87% of participants were already taking some form of antihypertensive therapy. Over a mean follow-up of 4.7 years, intensive therapy achieved an SBP

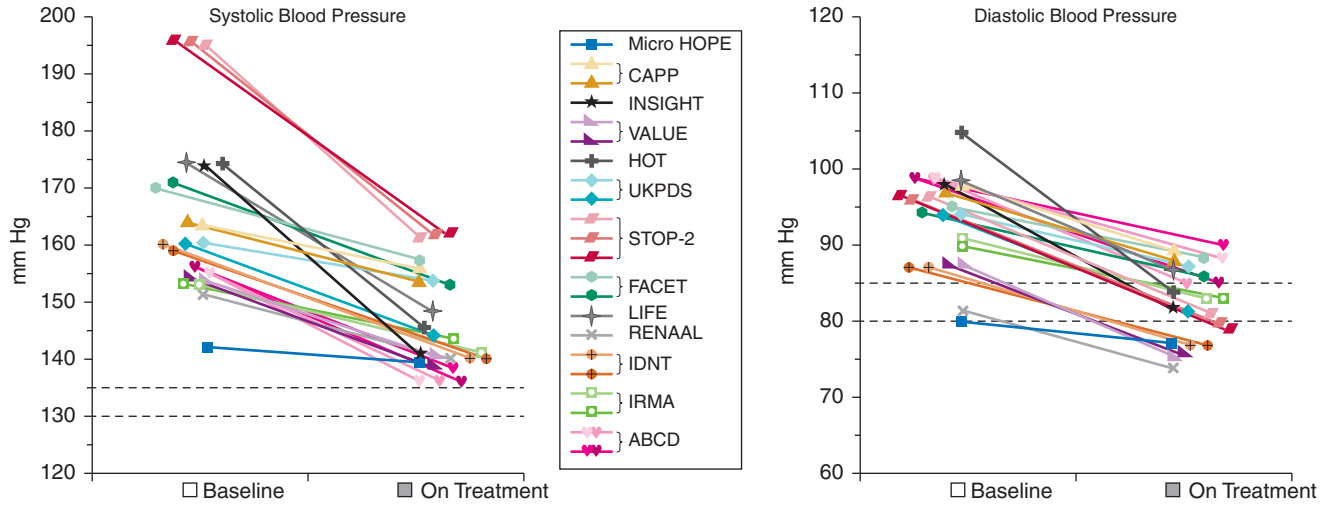


FIGURE 14-5 Effects of BP-lowering treatment on systolic and diastolic BP in patients with diabetes and hypertension in a number of trials before the ADVANCE and ACCORD trials. Values at trial entry and during treatment are shown for each trial. Dashed horizontal lines refer to goal BP values indicated by contemporary guidelines to be achieved during treatment. *(Reproduced with permission from Mancia G, Grassi G: Systolic and diastolic blood pressure control in antihypertensive drug trials,* J Hypertens *20:1461-1464, 2002.)*

of 119 mm Hg compared with 134 mm Hg in the standard therapy group, resulting in a mean between-group difference of 14.2 mm Hg. Despite this difference in SBP, intensive therapy did not result in a statistically significant reduction in major cardiovascular events (relative risk reduction [RRR] 12%; 95% CI −6 to 27%; $P=0.20$) (**Fig. 14-6**). When the components of the composite outcome were considered separately, intensive therapy did not reduce major coronary events (which included unstable angina) or cardiovascular death, but significantly reduced major strokes by 41% (95% CI 11%-61%). There was no statistically significant effect of intensive BP therapy on all-cause mortality or heart failure. There was no evidence of heterogeneity in treatment effect in subgroups of participants defined by age, sex baseline history of cardiovascular disease, and use of BP-lowering therapy at study entry.

Many have interpreted the ACCORD trial as being "negative" with respect to the BP-lowering component, stimulating discussion that the current target of 130/80 mm Hg or lower promulgated by many guidelines may not be justified. However, notwithstanding the clear benefits of a more aggressive approach to BP lowering for stroke well below this threshold, the 95% CIs around the estimates of effect size for other cardiovascular events, including CHD, do not exclude substantial and clinically important beneficial effects (approximately one-quarter reduction, which would be broadly consistent with a 14-mm Hg difference in SBP based on epidemiologic data). It is important to note that with the event rates in the control arm of ACCORD being approximately one half those anticipated, the trial was ultimately substantially underpowered. Intensive BP lowering in ACCORD was associated with an increased number of serious adverse events attributed to BP-lowering drugs, compared with the standard therapy group; however, overall rates over an average period of almost 5 years of follow-up were low (3.3% versus 1.3%). Particular concerns have been raised about higher levels of serum creatinine and lower levels of estimated glomerular filtration rate postrandomization among intensive–BP treatment participants. This did not translate to differences in end-stage renal disease (2.5% versus 2.4%), and intensive BP-lowering therapy was associated with the development of numerically fewer cases of microalbuminuria and macroalbuminuria, the latter being significantly lower than the rates observed in the standard therapy group.

Legacy Effects of Blood Pressure Lowering

In 2008, the UKPDS study reported data from post-trial annual follow-up for an additional 6 years undertaken for all study participants, without attempts to maintain therapies based on the original randomization.[37,38] Long-term post-trial observational follow-up of the blood glucose–lowering arm demonstrated sustained, and in some cases newly emerged, reductions in clinical events associated with original randomization to intensive glucose control.[38] (See also **Chapter 13**.) These benefits were observed despite convergence of HbA1c values within a year of post-trial monitoring. Similarly, the BP difference achieved between randomized arms during the trial was no longer apparent within 2 years of the longer-term follow-up.[37] However, unlike the blood glucose intervention, the significant reductions in clinical events were lost during the additional observational period, without the emergence of any new benefits. A reasonable interpretation of these findings is that BP reduction needs to be maintained for the long-term benefits of such treatment to continue.

New Drugs

In addition to relatively recent approvals of the direct renin inhibitor aliskiren and the angiotensin II type 1 receptor (AT1R) blocker azilsartan, a number of novel BP-lowering compounds are currently in clinical testing.[39] These include dual-action AT1R inhibitors that also block either neutral endopeptidase or the endothelin A receptor; a dual inhibitor of neutral endopeptidase and endothelin-converting enzyme; an aldosterone synthase inhibitor; an antagonist of natriuretic peptide receptor A; and a soluble epoxide hydrolase inhibitor. As clinical data accumulate, the efficacy and comparative efficacy of the molecules that proceed to approval may be examined in the specific context of T2DM.

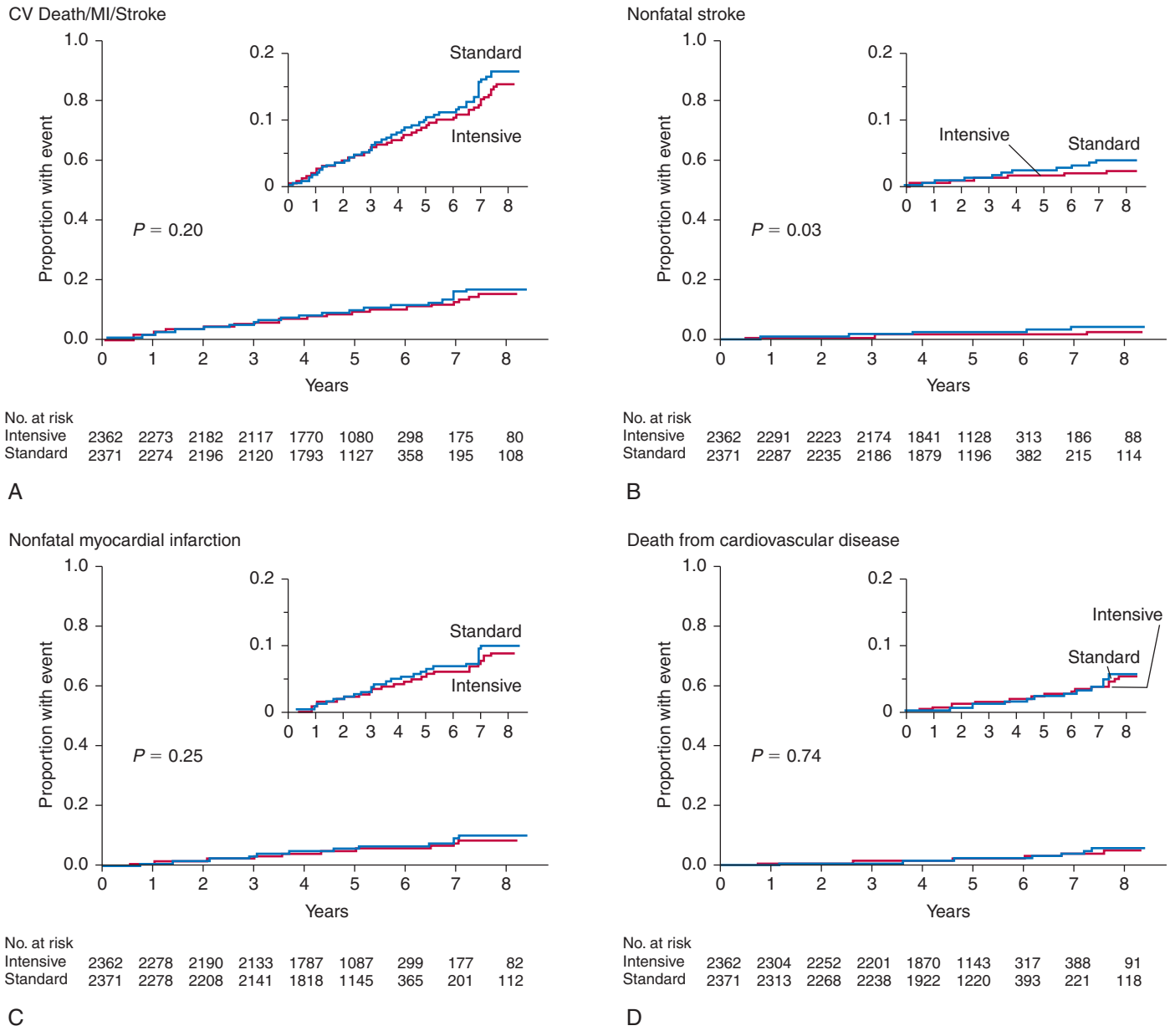


FIGURE 14-6 Kaplan-Meier curves for the primary composite outcome and its individual components in the ACCORD study. The insets show close-up versions of the graphs in each panel. CV = Cardiovascular; MI = myocardial infarction *(From ACCORD Study Group; Cushman WC, Evans GW, Byington RP, et al: Effects of intensive blood-pressure control in type 2 diabetes mellitus,* N Engl J Med *362:1575-1585, 2010.)*

EFFICACY AND SAFETY OF RENAL SYMPATHETIC DENERVATION

A recently developed therapeutic approach for the treatment of hypertension is endovascular catheter technology that allows selective sympathetic denervation of the kidney by transluminal radiofrequency ablation.[40] To date, the evaluation of efficacy and safety of this approach has been limited to populations with "resistant" primary hypertension, with persistently high levels of BP despite comprehensive combination drug therapy. The Symplicity HTN-2 trial is the first and only randomized study reported to date, including 106 patients (approximately 30% with T2DM) with baseline SBP levels of 160 mm Hg or greater (≥150 mm Hg in the presence of diabetes), despite the use of at least three BP-lowering agents. The between-group difference in the primary outcome of office-measured BP level at 6 months was large and highly statistically significant (33/11 mm Hg, $P < 0.0001$).[41] No separate analyses were performed in the subgroup with T2DM. No serious safety concerns were identified in this small study, but larger studies are under way and new studies in patients with milder forms of hypertension are being planned. Such studies may include a focus on patients with T2DM; in the meantime, renal sympathetic denervation is best described as a highly promising intervention requiring more reliable data on long-term efficacy and safety. Its applicability to the vast majority of patients with diabetes and hypertension globally, who have limited access to basic drugs, is a broader debate that will also take place.

SUMMARY

Available evidence about the effect of BP management on CHD risk in patients with T2DM can be reasonably summarized in the following way.



Lifestyle interventions (targeting physical activity and dietary modification) in people with T2DM can favorably affect BP levels, and trials powered to assess effects on clinical outcomes are ongoing. However, effective implementation strategies to enact sustained positive lifestyle changes—including for dietary sodium restriction, which is likely to be particularly important—are generally lacking.

Placebo-controlled trials provide clear evidence that BP lowering among individuals with diabetes and hypertension results in a reduction in CHD incidence. The findings of the most recent and largest of these trials suggest that routine provision of BP-lowering therapy to patients with T2DM, regardless of initial BP level, is an effective strategy for reducing CHD risk.

Debate about comparative efficacy of BP-lowering drugs for the prevention of CHD in patients with diabetes continues. Although not unequivocal, there are some data to support additional benefits of ACE inhibitor–based regimens over others for the outcome of CHD.

Specifically for the outcome of CHD, trial evidence of the benefits of more intensive versus less intensive BP lowering is consistently suggestive, but not definitive to date. The ACCORD trial failed to show clear benefits on CHD of aggressive management to a SBP target of below 120 mm Hg, compared with an SBP target of 140 mm Hg or lower, but this comparison was underpowered to exclude sizeable, clinically important effects.

These conclusions, however, should be considered in the context of a number of important points. First, recommendations about BP-lowering treatment must take into account the known or likely effects on all relevant health outcomes and not just CHD. For example, the evidence that more intensive versus less intensive BP lowering provides greater protection against stroke in patients with or without diabetes is unequivocal, including large beneficial effects in preventing stroke observed in the ACCORD trial. Similarly, calcium channel blocker or thiazide-based regimens may be more important for the prevention of stroke, whereas ACE-inhibitor or ARB-based regimens are more protective against the microvascular renal complications of diabetes. The use of beta blockers might be regarded as essential in patients with prior myocardial infarction or systolic heart failure. Thus, consideration of a number of individual patient characteristics that may be relevant to a broad range of clinical outcomes would be appropriate in making choices about the use of particular BP-lowering drug regimens in patients with T2DM.

Second, and related to this, is an understanding of the general paradigm of using an assessment of an individual's projected absolute risk of developing CHD (or stroke, or any cardiovascular disease) to help guide therapy. In the context of T2DM, this might be most relevant where uncertainty exists about the balance of potential risks and benefits in relation to the intensity of BP lowering in an individual patient. There are a number of clinical tools available to estimate CHD or CVD risk in people with T2DM, derived either from general populations or from specific populations with diabetes.[42–45] All have potential limitations including in relation to generalizability; nonetheless, these remain useful for clinical practice.[46,47]

Finally, any ongoing uncertainty about the relative efficacy of therapeutic regimens or appropriate targets for BP reduction in people with T2DM closer to the "normotensive" range is dwarfed by the lack of knowledge about effective strategies to ensure that people with T2DM receive any BP-lowering therapy in the first place, let alone what might be considered ideal regimens or acceptable levels of BP control. The "practice gaps" are very large, particularly in the low- and middle-income countries that have the highest numbers of people with T2DM, but also in countries with rich economies.[48–54] From a global perspective, these issues will not be addressed by new clinical trials establishing the efficacy of new drugs or new combinations of drugs. Rather, the development, implementation, and rigorous evaluation of interventions at the level of policy, systems, and services will be crucial to ensure maximal gains in human health from what we already know about the treatment of BP in people with T2DM.

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15 Effect of Lipid Management on Coronary Heart Disease Risk in Patients with Diabetes



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OVERVIEW

This chapter describes strategies for and effects of therapeutic lifestyle changes and/or pharmacologic interventions with lipid-lowering medications on coronary heart disease (CHD) risk in patients with diabetes mellitus (DM), focusing on the most recent data from randomized clinical trials in the context of contemporary clinical care.

Planning a strategy to manage dyslipidemia for CHD risk reduction for patients with DM can be partitioned into five steps: (1) identifying lipid-related risk factors for CHD, including those related to unhealthy lifestyle behaviors; (2) assessing and then stratifying CHD risk; (3) determining which among these risk factors are modifiable through interventions affecting lifestyle combined with timely and appropriate medications; (4) confirming effectiveness of various lipid interventions on CHD outcome reduction in clinical trials; and (5) translating the expected gains to common, unselected DM patients most likely to benefit from these interventions.

Coronary Heart Disease Risk Among Patients with Diabetes and Dyslipidemia

To better understand CHD risk for patients with versus without DM in the context of lipid management, it is informative to analyze baseline characteristics of DM patients participating in landmark lipid-lowering clinical trials such as trials focused exclusively on patients with DM, or those that report data on a sufficient number of patients making up DM subgroups. For the present summary, data were considered from trials with a high proportion of patients with DM at baseline (>15%) and/or trials that enrolled at least 100 patients with prevalent DM. Data from 47 lipid trials comprising 198,930 patients, of whom 65,558 had prevalent DM, are summarized in **Tables 15-1** (alphabetically by trial name acronym) and **15-2** (ordered by descending numbers of participants with DM), with abbreviations used to describe respective trial outcomes defined in **Table 15-3**.[1–82] Except for the Acute Coronary Syndrome Israeli Survey (ACSIS),[9] all studies were randomized controlled trials, most of which evaluated monotherapy with a statin or a fibrate versus placebo. A few randomized controlled trials studied a combined lipid-lowering intervention (statin plus fibrate; statin plus ezetimibe); Steno-2 was a randomized comparison of a multifactorial intervention versus usual care, with statins and/or fibrates used as part of a comprehensive global cardiovascular disease (CVD) risk intervention strategy in patients with DM and albuminuria.[73]

The baseline characteristics of patients participating in clinical trials and substudies that included only patients with DM (n = 46,326 patients) are described in **Table 15-4**, and ranked by baseline low-density lipoprotein (LDL) cholesterol (LDL-C). Mean age at entry was 60.3 years and, similar to lipid intervention trials not focusing specifically on DM, men accounted for more than two thirds of the patients. Most DM patients in these studies are assumed to have had type 2 diabetes mellitus (T2DM) given the relative prevalence of T2DM versus type 1 diabetes mellitus (T1DM) in the age groups studied (see **Chapter 1**), with a few trials specifically allowing inclusion of patients with T1DM, and most trials not differentiating DM type for eligibility.

Average baseline lipid levels in the trials surveyed did not meet contemporary targets for lipid management in DM patients (see later), with mean LDL-C 129 mg/dL (3.3 mmol/L); non–high-density lipoprotein (HDL) cholesterol (non–HDL-C)

TABLE 15-1 Trials on Lipid Management of Coronary Heart Disease (CHD) Risk

ACRONYM	REFERENCES	STUDY NAME	IDENTIFIER	PHARMACEUTICAL SPONSOR (S)/LLD(S) SUPPLIERS
4D	1	Die Deutsche Diabetes Dialyse studie		Pfizer
4S	2-4	Scandinavian Simvastatin Survival Study		Merck
4S (substudy)	4	Scandinavian Simvastatin Survival Study (diabetes substudy)		Merck
A to Z	5	Aggrastat to Zocor		Merck
ACCORD-Lipid	6-8	Action to Control Cardiovascular Risk in Diabetes - Lipid arm	NCT00000620	Abbott; Amylin Ph.; AstraZeneca; Bayer; GSK; King Ph.; Merck; Novartis; NovoNordisk; SanofiAventis; Takeda
ACCORD-Lipid (AD subgroup)	7	Action to Control Cardiovascular Risk in Diabetes - Lipid arm (AD subgroup)	NCT00000620	same as above
ACSIS	9	Acute Coronary Syndrome Israeli Surveys Data		
AFCAPS/TexCAPS	10,11	Air Force/Texas Coronary Atherosclerosis Prevention Study		Merck
AIM-HIGH	12,13	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes	NCT00120289	Abbott; Merck
ALERT	14	Assessment of Lescol in Renal Transplantation		Novartis
ALLHAT-LLT	15	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial	NCT00000542	AstraZeneca; Bristol-Myers Squibb; Pfizer
ASCOT-LLA	16, 17	Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm		Pfizer; Servier; Leo; Solvay
ASCOT-LLA (substudy)	17	Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (diabetes substudy)		Pfizer; Servier; Leo; Solvay
ASPEN	18	Atorvastatin as Prevention of CHD Endpoints in patients with Non-insulin dependent diabetes mellitus		Pfizer
AURORA	19, 20	A Study to Evaluate the Use of Rosuvastatin in Subjects or Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events	NCT00240331	AstraZeneca
AURORA (substudy)	20	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events (diabetes substudy)	NCT00240331	AstraZeneca
AVERT	21	Atorvastatin Versus Revascularization Treatment		Parke-Davis
BIP	22, 23	Bezafibrate Infarction Prevention		Boehringer Mannheim
CARDS	24	Collaborative Atorvastatin Diabetes Study	NCT00327418	Pfizer
CARE	25-27	Cholesterol and Recurrent Events		Bristol-Myers Squibb
CARE (substudy)	27	Cholesterol and Recurrent Events (diabetes substudy)		Bristol-Myers Squibb
DAIS	28, 29	Diabetes Atherosclerosis Intervention Study		Fournier
DIS	30	Diabetes Intervention Study		VEB Berlin
Extended-ESTABLISH	31	Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis during Half a Year After Coronary Event		
FIELD	32-34	Fenofibrate Intervention and Event Lowering in Diabetes	ISRCTN64783481	Fournier
FIELD (AD subgroup)	32, 33	Fenofibrate Intervention and Event Lowering in Diabetes (AD subgroup)	ISRCTN64783481	Fournier
FIELD (MetS subgroup)	34	Fenofibrate Intervention and Event Lowering in Diabetes (MetS subgroup)	ISRCTN64783481	Fournier
GISSI-Prevenzione	35	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico - Prevenzione		
GREACE	36, 37	Greek Atorvastatin and Coronary-heart-disease Evaluation		
GREACE (substudy)	37	Greek Atorvastatin and Coronary-heart-disease Evaluation - subgroup with diabetes		
HHS	38, 39	Helsinki Heart Study		Warner-Lambert

HHS (substudy)	39	Helsinki Heart Study (diabetes substudy)		Warner-Lambert
HPS—MRC/BHF	40, 41	Medical Research Council and British Heart Foundation Heart Protection Study		Merck
HPS—MRC/BHF (substudy)	41	Medical Research Council and British Heart Foundation Heart Protection Study (diabetes substudy)		Merck
HPS2-THRIVE	42	Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events	NCT00461630	Merck
IDEAL	43, 44	Incremental Decrease in End Points Through Aggressive Lipid Lowering	NCT00159835	Pfizer
IMPROVE-IT	45	Improved Reduction of Outcomes: Vytorin Efficacy International Trial: Comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes	NCT00202878	Merck; Shering Plough
JAPAN-ACS	46	Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome	NCT00242944	Kowa
LDS	47	Lipids in Diabetes Study		Bayer
LEADER	48, 49	Lower Extremity Arterial Disease Event Reduction	ISRCTN41194621	Boehringer Mannheim
LIPID	50-52	Long-term Intervention with Pravastatin in Ischaemic Disease		Bristol-Myers Squibb
LIPS	53	Lescol Intervention Prevention Study		Novartis
MEGA	54	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese	NCT00211705	Sankyo
MIRACL	55-57	Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering		Parke-Davis
PACT	58	Pravastatin in Acute Coronary Treatment		Bristol-Myers Squibb
Post-CABG (FU)	59, 60	Post Coronary Artery Bypass Graft		Merck; Bristol-Myers Squibb
PROACTIVE	61, 62	Prospective Pioglitazone Clinical Trial in Macrovascular Events		Takeda; Eli Lilly
PROSPER	63	Prospective Study of Pravastatin in the Elderly at Risk		Bristol-Myers Squibb
PROVE IT–TIMI 22	64-66	Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22		Bristol-Myers Squibb; Sankyo
PROVE IT–TIMI 22 (substudy)	65	Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (diabetes substudy)		Bristol-Myers Squibb; Sankyo
REVEAL	67	Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification	NCT01252953	Merck
REVERSAL	68	Reversal of Atherosclerosis with Aggressive Lipid Lowering	NCT00380939	Pfizer
SENDCAP	69	St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention study		Boehringer Mannheim
SHARP	70	Study of Heart and Renal Protection	NCT00125593	Merck; Shering Plough
SPARCL	71, 72	Stroke Prevention by Aggressive Reduction of Cholesterol Levels	NCT00147602	Pfizer
SPARCL (substudy)	72	Stroke Prevention by Aggressive Reduction of Cholesterol Levels (diabetes substudy)	NCT00147602	Pfizer
Steno-2	73	Steno-2 Study	NCT00320008	Novo-Nordisk
TNT	74-78	Treating to New Targets study	NCT00327691	Pfizer
TNT (substudy)	78	Treating to New Targets study (diabetes study)		Pfizer
VA-HIT	79-81	Veterans Affairs High-Density Lipoprotein Intervention Trial	NCT00283335	Parke-Davis
VA-HIT (substudy)	81	Veterans Affairs High-Density Lipoprotein Intervention Trial (diabetes substudy)	NCT00283335	Parke-Davis
VA Cooperative Study	82	Veteran Administration Cooperative Study of Atherosclerosis, Neurology Section		

TABLE 15-2 Trials of Lipid-Lowering Therapy by Numbers of Diabetic Patients at Inclusion

ACRONYM	PUBLICATION YEAR	CHD RISK	PATIENTS (n)	DIABETES (n)	DIABETES (%)	THERAPY	CHD-RELATED OUTCOMES*
FIELD	2005	PP and SP	9795	9795	100	Fibrate	C; B+D+I+M
FIELD (MetS SS)	2009	PP and SP	8183	8183	100	Fibrate	C; B+D+I+M
HPS—MRC/BHF	2002	PP and SP	20,536	5963	29	Statin	C; A+G
HPS—MRC/BHF (DSS)	2003	PP and SP	5963	5963	100	Statin	E+B
ACCORD—Lipid	2010	PP and SP	5518	5518	100	Fibrate	C; J+D
PROACTIVE	2005	SP	5238	5238	100	Glitazone	C; A+J+H+M
LDS	ET	PP	4026	4026	100	Statin and/or fibrate	C; K+P+J+M
ALLHAT-LLT	2002	PP and SP	10,355	3638	35	Statin	A
ACSIS	2012	ACS	8982	3063	34	Fibrate	C; A+I+L+M
CARDS	2004	PP	2838	2838	100	Statin	C; H+M+T
ASCOT-LLA	2003	PP	10,305	2532	25	Statin	J+G
ASCOT-LLA (DSS)	2005	PP	2532	2532	100	Statin	B
ASPEN	2006	PP	2410	2410	100	Statin	C; D+J+M+O+L
SHARP	2011	PP and SP	9270	2094	23	Statin and ezetimibe	C; J+G+M
FIELD (AD subgroup)	2009	PP and SP	2014	2014	100	Fibrate	C; B+D+I+M
MEGA	2006	PP	7832	1632	21	Statin	C; I+L+M+P
TNT	2005	SP	10,001	1501	15	Statin	C; G+J+O+T
TNT (DSS)	2006	SP	1501	1501	100	Statin	C; G+J+O+T
4D	2005	PP and SP	1255	1255	100	Statin	C; D+J
AIM-HIGH	2011	SP	3414	1158	34	Niacin	C; G+J+H+M
A to Z	2004	ACS	4497	1059	24	Statin	C; D+J+H
IDEAL	2005	SP	8888	1057	12	Statin	C; G+J+O
PROVE IT–TIMI 22 (DSS)	2006	ACS	978	978	100	Statin	C; A+I+L+M
ACCORD-Lipid (AD SS)	2010	PP and SP	941	941	100	Fibrate	C; J+D
SPARCL	2006	SP	4731	794	17	Statin	
SPARCL (DSS)	2011	SP	794	794	100	Statin	
LIPID	1998	SP	9014	782	9	Statin	G
VA-HIT	1999	SP	2531	769	30	Fibrate	C; J+G
VA-HIT (DSS)	2002	SP	769	769	100	Fibrate	C; J+G
DIS	1991	PP	761	761	100	Fibrate	E
PROVE IT–TIMI 22	2004	ACS	4162	734	18	Statin	C; A+I+L+M
AURORA	2009	PP and SP	2776	731	26	Statin	C; J+D
AURORA (DSS)	2011	PP and SP	731	731	100	Statin	C; G+J
MIRACL	2001	ACS	3086	715	23	Statin	C; A+J+O+L
PROSPER	2002	PP and SP	5804	623	11	Statin	C; G+J
CARE	1998	SP	4159	586	14	Statin	G+J
CARE (DSS)	1998	SP	586	586	100	Statin	G+J+M
GISSI-Prevenzione	2000	SP	4271	582	14	Statin	C; A+I
PACT	2004	ACS	3408	478	14	Statin	C; A+I+L
DAIS	2001	PP and SP	418	418	100	Fibrate	R
ALERT	2003	PP and SP	2102	396	19	Statin	C; G+J+M
GREACE	2002	SP	1600	313	20	Statin	C; A+J+L+Q+M
GREACE (DSS)	2003	SP	313	313	100	Statin	C; A+J+L+Q+M
BIP	2000	SP	3090	309	10	Fibrate	C; K+J+P
LEADER	2002	PP and SP	1568	268	17	Fibrate	E
4S	1994	SP	4444	202	5	Statin	A
4S (DSS)	1997	SP	202	202	100	Statin	A

TABLE 15-2 Trials of Lipid-Lowering Therapy by Numbers of Diabetic Patients at Inclusion—cont'd

ACRONYM	PUBLICATION YEAR	CHD RISK	PATIENTS (n)	DIABETES (n)	DIABETES (%)	THERAPY	CHD-RELATED OUTCOMES*
LIPS	2002	SP	1677	202	12	Statin	C; G+J+M
SENDCAP	1998	PP	164	164	100	Fibrate	
Steno-2	2008	PP and SP	160	160	100	Statin and/or fibrate	A
AFCAPS/TexCAPS	1998	PP	6605	155	2	Statin	C; E
HHS (DSS)	1992	PP	135	135	100	Fibrate	C; K+J+G
VA Cooperative Study	1973	SP	532	128	24	Fibrate	A+B
Post-CABG (FU)	2000	SP	1351	116	9	Statin	C; D+J+M
HHS	1987	PP	4081	108	3	Fibrate	C; K+J+G
REVERSAL	2004	SP	502	95	19	Statin	R
JAPAN-ACS	2009	SP	252	74	29	Statin	R
Extended-ESTABLISH	2010	ACS	180	66	37	Statin	C; A+H
AVERT	1999	SP	341	52	15	Statin	E
Total (n)			198,930	65,558			

ACS = Acute coronary syndrome; AD = atherogenic dyslipidemia; DSS = diabetes substudy; ET = early termination; FU = follow-up; LLA = lipid-lowering arm; LLT = lipid-lowering therapy; MetS = metabolic syndrome; PP = primary prevention; SP = secondary prevention; SS = substudy.
*See **Table 15-1** for acronym definition and **Table 15-3** for outcome categories.

TABLE 15-3 Outcomes Classification

CATEGORIES	DESCRIPTION	CODE
Total mortality	All-cause death	A
CV composite	All CV events (including procedures)	B
	MACE	C
	CV death	D
Cardiac	Total CHD and major coronary events	E
	Nonfatal CHD	F
	Cardiac death or fatal CHD	G
	ACS or ACE	H
	All MI	I
	Nonfatal MI	J
	Fatal MI	K
	Unstable or hospitalization-requiring AP	L
	Coronary revascularization (PCI or CABG)	M
	Life-threatening arrhythmias	N
	Resuscitation for cardiac arrest	O
	Sudden death	P
	CHF	Q
Coronary imaging	Angiographic CAD progression, change in coronary atheroma volume	R
Cerebrovascular	All major cerebrovascular events	S
	All stroke and TIA	T
	Nonfatal stroke	U
	Fatal stroke	V
	Carotid revascularization	W
CV composite	Non-CHD MACE	X
Other mortality	Non-CHD CV death	Y
Peripheral	Any PAD event (including revascularization and leg amputation)	Z

ACE = acute coronary event; AP = angina pectoris; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

166 mg/dL (4.3 mmol/L); HDL-C 42 mg/dL (1.1 mmol/L); and triglycerides (TGs; triacylglycerols) 180 mg/dL (2.0 mmol/L). In most diabetes trials and DM subgroup analyses, LDL-C was calculated, with routine direct measurement in only three studies: 4D; HPS—MRC/BHF (DM subgroup); and PROACTIVE.[1,41,61,62] Mean baseline apolipoprotein B100 (apo B) concentration was 115 mg/dL, a value also beyond generally accepted targets, as inferred from studies in which baseline apo B level was available in the reports.*

In addition to elevated and/or unsatisfactory LDL-C levels at study entry, the frequent findings of low HDL-C together with elevated fasting TGs are consistent with the assumption of a high prevalence of atherogenic dyslipidemia in these DM patients at enrollment (see **Table 15-4** and **Chapter 10**). Similarly, data from studies in which baseline apo B was measured concomitantly with LDL-C reveal a high prevalence of increased small, dense LDL particles—a pattern commonly observed in T2DM (see **Chapter 10**).[83–93]

Given the high cardiovascular (CV) risk associated with DM (see **Chapters 7**, **9**, and **10**), observed event rates in reported lipid trials are influenced by the proportion of patients with DM enrolled. The rates of primary CV outcome events among patients with DM across lipid intervention trials in primary prevention, secondary prevention, and post–acute coronary syndrome (ACS) patient populations are summarized in **Table 15-5**, arranged by decreasing hazard, with significantly higher rates among those with versus without DM across the spectrum of clinical indication.

To estimate CHD risk or to better characterize it for specific patients groups, there are other complementary determinations in addition to total cholesterol and LDL-C levels measurements. Non–HDL-C, apo B, and LDL particle (LDL-P) concentration are closely associated with obesity, DM, insulin resistance or hyperinsulinemia, and other markers of dysmetabolism in conditions of increased cardiometabolic risk, such as T2DM. Their determination, in addition to

*References 24, 28, 29, 32-34, 41, 65, 69, 72, 78.

TABLE 15-4 Baseline Characteristics of Diabetes Trials and Substudies Ranked by Low-Density Lipoprotein (LDL) Cholesterol (LDL-C) at Inclusion

ACRONYM	PATIENTS (n)	MALES (%)	WHITE CAUCASIANS (%)	MEAN AGE (YR)	INCLUSION CRITERIA	DM TYPE	DM DURATION (years)	HBA1C (%)	TC	NON–HDL-C	apo B	LDL-C	HDL-C	TG
HHS (DSS)	135	100	Most	49	Non–HDL-C ≥200 mg/dL	T2DM	4.5		292	246		200	46	214
GREACE (DSS)	313	56	Most	55	Prior MI or >70% stenosis in one or more vessels; TC >100; TGs <400 mg/dL	T2DM (92%)	10.5	7.5	271	236		189	35	221
4S (DSS)	202	78	Most	60	MI or angina; TC 213-309 mg/dL; TGs <221 mg/dL	DM			259	216		186	43	150
SENDCAP	164	71	56	51	T2DM; no CV history	T2DM	5	9.5	223	184	131	142	39	198
CARE (DSS)	586	80	85	61	MI history; TC <240 mg/dL; LDL-C 115-174 mg/dL; TG <350 mg/dL	DM			206	168		136	38	164
Steno-2	160	74	Most	55	T2DM with microalbuminuria	T2DM	5.8	8.6	210	170		133	40	159
DAIS	418	73	96	57	T2DM with CAD	T2DM	8.6	7.5	215	176	116	131	39	229
SPARCL (DSS)	794	61		64	Diabetes and stroke or TIA	T2DM			208	162	134	131	46	155
ASCOT-LLA (DSS)	2532	76	90	64	T2DM with HBP; no CHD; ≥3 CV RF's	T2DM			205	159		128	46	168
4D	1255	54	Most	66	T2DM; ESRD on hemodialysis	T2DM	18	6.7	218	182		125	36	261
HPS—MRC/BHF (DSS)	5963	70	Most	62	Diabetes	T2DM (90%)	27	7	220	179	110	124	41	204
LDS	4026	75	91	61	LDL-C 58-155 mg/dL; TG <400 mg/dL	T2DM	6	8	174	128		120	46	133
FIELD	9795	63	Most	62	T2DM; TC 116-251 mg/dL and TC/HDL-C ≥4 or TG 89-443 mg/dL	T2DM	5	6.9	195	152	97	119	43	173
CARDS	2838	68	95	62	T2DM; low or normal LDL-C; at least one of: DRP; albumin; smoking; HBP	T2DM	8	7.9	207	153	117	117	54	173
PROACTIVE	5238	66	99	62	T2DM with macrovascular disease	T2DM	9.5	8.1	199	154		114	45	198
ASPEN	2410	66	84	61	T2DM; LDL-C above contemporary guidelines	T2DM	8	7.8	194	147		113	47	147
VA-HIT (DSS)	769		14	65	Diabetes plus CHD; HDL-C ≤40 mg/dL; LDL-C ≤140 mg/dL	DM			172	141		108	31	166
PROVE IT–TIMI 22 (DSS)	978	72	85	60	Post-ACS status	DM			178	140	100	101	38	171
ACCORD-Lipid	5518	69	69	62	T2DM; high CV risk	T2DM	10	8.3	175	137		100	38	164
AURORA (DSS)	731	66	76	65	DM patients with ESRD on chronic hemodialysis	DM			174	131		97	43	168
TNT (DSS)	1501	73	89	63	DM and stable CHD; LDL-C <130 mg/dL	DM	8.5	7.4	175	130	113	96	45	171
Total	46326													
Mean		70.6		60.3			9.6	7.8	208	166	115	129	42	180

All lipid values in mg/dL.

See **Table 15-1** for acronym definitions and **Table 15-2** for primary outcome descriptions.

apo B = Apolipoprotein B100; DRP = diabetic retinopathy; ESRD = end-stage renal disease; HbA1c = glycated hemoglobin A1c; HBP = high blood pressure; HDL-C = high-density lipoprotein cholesterol; RF = risk factor; T2DM = type 2 diabetes mellitus, TC = total cholesterol; TG = triglycerides (triacylglycerols).

TABLE 15-5 Primary Outcome Rates (Comparator Arm), Baseline Atherogenic Lipids, and apo B from Lipid-Lowering Trials

TRIALS WITH DIABETIC SUBPOPULATIONS AT ENTRY							DIABETES TRIALS AND DIABETES SUBSTUDIES						
	Age (yr)	Diabetes (%)	Non–HDL-C	LDL-C	apo B	Primary Outcome (% per yr)		Age (yr)	Diabetes (%)	Non–HDL-C	LDL-C	apo B	Primary Outcome (% per yr)
Acute Coronary Syndrome													
ACSIS	63	34	168	96		75.0	PROVE IT–TIMI 22 (DSS)	60	100	140	101	100	15.9
MIRACL	65	23	159	124	132	56.1							
PACT	61	14				15.5							
PROVE IT–TIMI 22	58	18	143	106	102	13.1							
A to Z	61	24	146	112		7.7							
ESTABLISH (FU)	62	37	137	115	86	7.1							
Secondary Prevention													
AVERT	59	15	179	143		13.9	GREACE (DSS)	55	100	236	189		10.1
GREACE		20	225	193		8.3	PROACTIVE	62	100	154	114		7.5
LIPS	60	12	162	131		6.8	CARE (DSS)	61	100	168	136		7.4
VA Cooperative Study	55	24				6.3	VA-HIT (DSS)	65	100	141	108		7.1
AIM-HIGH	64	34	111	74	83	5.4	4S (DSS)	60	100	216	186		4.6
Post-CABG (FU)	62	9	187	156		5.4	TNT (DSS)	63	100	130	96	113	3.7
VA-HIT	64	30	143	111	96	4.3							
GISSI-Prevenzione	60	14	183	152		3.1							
CARE	59	14	170	139		2.6							
BIP	60	10	177.4	148		2.4							
TNT	61	15	128	97	111	2.2							
IDEAL	62	12	151	122	119	2.2							
4S	59	5	214	188		2.1							
LIPID	62	9	182	150	133	1.4							
Primary and Secondary Prevention													
AURORA	64	26	131	100	82	7.8	AURORA (DSS)	65	100	131	97		10.8
LEADER	68	17	172	131		5.2	4D	66	100	182	125		9.6
PROSPER	75	11	170	147		5.1	HPS—MRC/BHF (DSS)	62	100	179	124	110	5.2
HPS—MRC/BHF		29	187	131	114	2.9	Steno-2	55	100	170	133		3.8
SHARP	62	23	146	107	92	2.7	ACCORD-Lipid (AD)		100				3.7
ALLHAT-LLT	66	35	176	146		2.6	ACCORD-Lipid	62	100	137	100		2.4
ALERT	50	19	197	158		2.5	FIELD	62	100	152	119	97	1.2
Primary Prevention													
AFCAPS/TexCAPS	58	2	184	150		1.1	ASPEN	61	100	147	113		3.8
ASCOT-LLA	63	25	162	131		0.9	ASCOT-LLA (DSS)	64	100	159	128		3.6
HHS	47	3	223	189		0.8	CARDS	62	100	153	117	117	2.3
MEGA	58	21	184	157		0.5	HHS (DSS)	49	100	246	200		2.1
							DIS	46	100				1.6

All lipid measurements represent baseline values (in mg/dL).
See **Table 15-1** for acronyms definition and **Table 15-2** for primary outcomes description.

LDL-C measurement, may provide information before and after introduction of lipid-lowering therapies, to assess CV risk at baseline and residual vascular risk after intervention. Compared with on-treatment LDL-C, these may help to clarify some aspects of risk and response to therapy, but their combined measurement is not routinely recommended in DM.

In addition to non–HDL-C, apo B, and LDL-P determination, screening for atherogenic dyslipidemia, before any lipid-lowering intervention, is an easy and inexpensive means to determine residual vascular risk associated with low HDL-C, high TGs, and their determinants. As a result of lack of agreement on cutoffs for HDL-C and TGs, this is rarely performed in routine practice. An alternative approach to defining atherogenic dyslipidemia as the combined occurrence of high TG levels plus low HDL-C uses the ratio of TG to HDL-C. Because both TG and HDL-C levels are continuous risk variables with mutually additive associations with residual vascular risk, computing a ratio of fasting TGs to HDL-C provides a summary metric for the severity of atherogenic dyslipidemia, calibrated as a continuous rather than a dichotomous variable. Given the extreme right skewness of TG values, assessing atherogenic dyslipidemia using log(TGs)/HDL-C may be more clinically informative than an untransformed ratio.[91,92]

LIPID MANAGEMENT STRATEGIES TO REDUCE CARDIOVASCULAR RISK

Therapeutic Lifestyle Changes

The cardiometabolic abnormalities underlying CHD risk in T2DM and their potentially reversible components under the influence of various therapeutic lifestyle changes make the population with these abnormalities particularly suitable to respond positively to such interventions, provided they are applied early (i.e., in primary prevention) and maintained long term (see **Chapters 5** and **12**). Long-term compliance with therapeutic lifestyle changes must be optimized and regularly assessed and reinforced, because it is often difficult for patients with DM to comply long term with dietary and lifestyle advice. This is all the more relevant because the hallmark of atherogenic dyslipidemia (low HDL-C and high TGs) and all three other defining components of the metabolic syndrome are responsive to therapeutic lifestyle changes (see **Chapters 4**, **5**, and **12**).

Lifestyle approaches and dietary strategies to lower LDL-C and TGs and raise HDL-C as well as the effects of dietary carbohydrate restriction on atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome have been previously reviewed.[94,95] The American Diabetes Association (ADA) recommends that DM patients on low-carbohydrate diets undergo lipid profile monitoring and that the ratios of dietary intake of carbohydrates, proteins, and fat be individually adjusted to the metabolic requirements and preferences of patients. With regard to dietary intake of saturated and *trans*-saturated fatty acids, both modulators of LDL-C levels, there are no specific data available for patients with DM, and recommended dietary goals for DM patients are currently those, by default, of individuals with established CHD. Thus, saturated fat intake should not exceed 7% of total calories, and intake of *trans*-saturated fatty acids should be reduced.[96]

Unfortunately, for most T2DM patients in real-life conditions it is very hard to follow the current recommendations regarding dietary and physical activity for DM for the long term and/or with the required intensity. This underscores the importance of systems-based lifestyle interventions (see **Chapter 12**). Even for those who are able to implement lifestyle changes, many will not achieve sufficiently low LDL-C, non–HDL-C, and apo B and/or improve atherogenic dyslipidemia components through therapeutic lifestyle changes alone and will require lifelong therapy with one or more lipid-lowering drugs. For example, in the Action for Health in Diabetes (Look AHEAD) trial, 5145 overweight or obese adults with T2DM were randomized to intensive lifestyle intervention focusing on weight loss and increased leisure-time physical activity versus standard care diabetes support and education.[97] Despite greater and sustained weight loss, greater reductions in glycated hemoglobin, and improvements in fitness in the intensive lifestyle arm, there was no difference achieved between the groups in LDL-C. The overall trial failed to demonstrate mortality improvement, as discussed in **Chapter 12**.

Drugs Targeting Low-Density Lipoprotein Cholesterol

Given the predominant role of LDL-C as the major lipid-related modifiable risk factor for CHD in nondiabetic and diabetic patients, most of the pivotal studies have investigated the benefit on CHD outcomes of pharmacologic agents whose main effect is to reduce LDL-C levels (**Fig. 15-1**). Most of the clinical evidence of a beneficial effect on CHD of a decrease in total cholesterol and/or LDL-C was derived from landmark clinical trials with statins in nondiabetic and diabetic cohorts. In contrast, it is currently not established whether other nonstatin drugs specifically targeting LDL-C (ezetimibe; bile acid binders; proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) (**Fig. 15-2**), or with an LDL-C– lowering component among other lipid- and lipoprotein-modulating

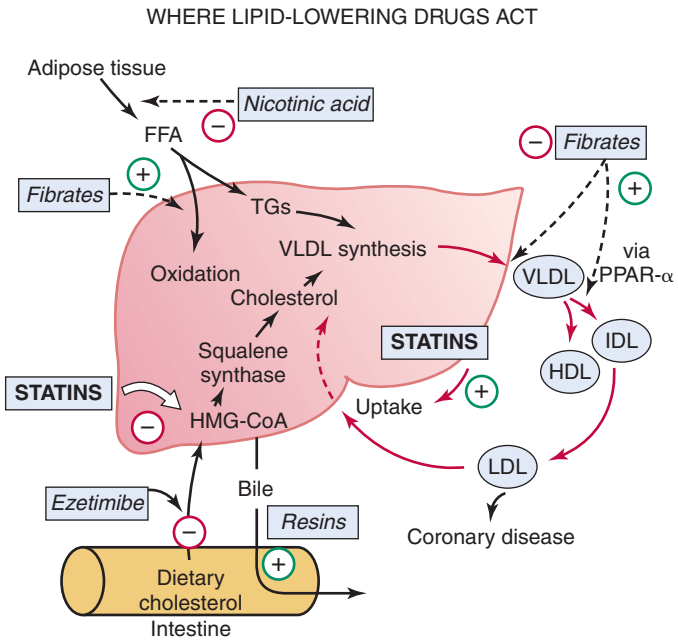


FIGURE 15-1 Sites of action of lipid-modifying drugs. Hepatic import and export of lipids is crucial to the sites of action of lipid-lowering drugs. Proposed mechanism of action of statins, fibrates, and nicotinic acid. FFA = Free fatty acid; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; IDL = intermediate-density lipoprotein; PPAR-α = peroxisome proliferator–activated receptor alpha; VLDL = very low-density lipoprotein. *(Figure copyright L.H. Opie, 2012. From Gotto AM, Opie LH:* Drugs for the Heart. *Philadelphia, Saunders, 2013, pp 398-435.)*

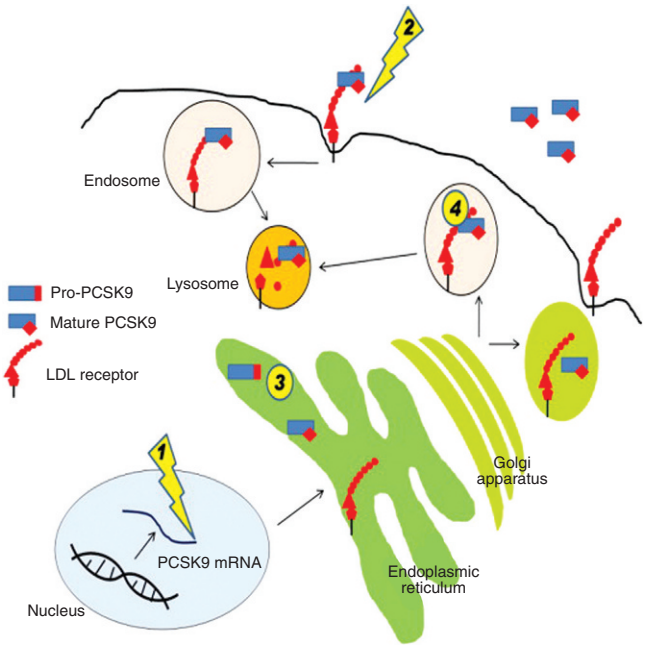


FIGURE 15-2 PCSK9 inhibition. Proprotein convertase subtilisin/kexin type 9 (PCSK9): from structure–function relation to therapeutic inhibition. *(From Tibolla G, Norata GD, Artali R, et al. Proprotein convertase subtilisin/kexin type 9 (PCSK9): from structure-function relation to therapeutic inhibition.* Nutr Metab Cardiovasc Dis *21:835-843, 2011.)*

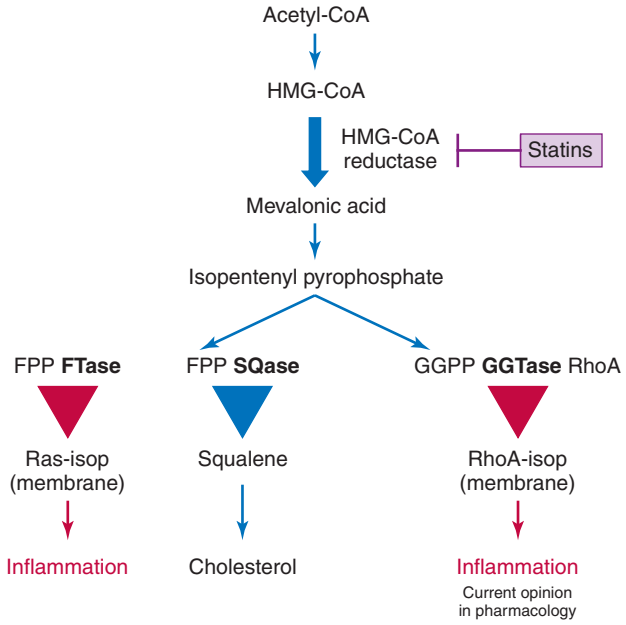


FIGURE 15-3 Mechanism of action of statins. The mechanism by which statins could be used for the treatment of COPD patients seems to be the same as that observed for cholesterol lowering. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; FPP = farnesyl pyrophosphate; FTase = farnesyl protein transferase; SQase = squalene synthase; GGPP = geranylgeranyl diphosphate; GGTase = geranylgeranyl protein transferase. *(From Matera MG, Calzetta L, Rinaldi B, et al. Treatment of COPD: moving beyond the lungs.* Curr Opin Pharmacol *12:315-22, 2012.)*

effects (niacin, fibrates) have a beneficial influence on cardiovascular events in nondiabetic or diabetic patients.

3-Hydroxy-3-Methylglutaryl-Coenzyme a (HMG-CoA) Reductase Inhibitors: the Statins

Statins inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, upregulating hepatic expression of LDL receptors and increasing uptake of circulating LDL (**Fig. 15-3**), and thereby decreasing circulating cholesterol (total cholesterol, LDL-C, and non–HDL-C) as a result of lowered LDL-P numbers. As a direct consequence, statins also reduce levels of apo B, the major atherogenic apolipoprotein, of which a single structural molecule is present on each LDL-P, as well as on each of their TG-rich lipoprotein precursors (very low-density lipoproteins [VLDLs]; intermediate-density lipoproteins [IDL]; and VLDL remnants).

In general, patients with and without diabetes respond similarly to statins with regard to LDL-C reduction, with response similarly dependent on drug choice, dose choice, and individual response. Proportional reductions in LDL-C levels on statin treatment range from 20% to 40% for less potent statins (fluvastatin, lovastatin, and pravastatin), 30% to 45% for simvastatin, and 40% to more than 50% for the most potent statins (atorvastatin, rosuvastatin, and pitavastatin). In the vast majority of diabetic and nondiabetic patients, long-term statin use is safe and effective.[98–108]

Patients with Diabetes in Key Statin Trials

Numerous studies have demonstrated the effectiveness of statins to reduce primary CHD outcomes in primary and secondary prevention settings and post-ACS events; the risk reduction after LDL-C lowering parallels the magnitude of the achieved LDL-C decrease in populations with and without diabetes. The studies having established the beneficial effect of statins on CHD risk in patients with DM selected for the present review comprised a total of 20,103 DM patients, followed for a mean duration of 4.0 years. Average (1 standard deviation) on-treatment LDL-C decreased to a mean 81 (standard deviation [SD] 18) mg/dL (2.1 [SD 0.5] mmol/L). This corresponds to absolute and relative reductions of 48 mg/dL (1.2 mmol/L) and 36%, respectively. With respect to non–LDL lipids, mean on-statin HDL-C was 46 (4) mg/dL (1.2 [0.1] mmol/L); non–HDL-C was 114 (19) mg/dL (3.0 [0.5] mmol/L); and TG was 144 (12) mg/dL (1.6 [0.1] mmol/L) (**Table 15-6**).

In the active arms of statin trials (n = 10,077), a total of 1638 primary outcome events (5.3%/year) were observed, versus 2022 outcomes (7.0 %/year) in the comparator arms (n = 10,026), with a weighted and adjusted hazard ratio (HR) of 0.76 (95% confidence interval [CI] 0.65 to 0.84) favoring statin treatment. As a class, for each 1 mg/dL (0.03 mmol/L) reduction in LDL-C achieved on statin, the HR of incident CHD was reduced on average by 0.5%. This translated into a 19.5% primary outcome reduction for every 1 mmol/L (40 mg/dL) decrease of LDL-C. The mean absolute risk reduction for composite major adverse CV events in statin trials was 6.0%; the mean relative risk reduction (RRR) was 25%. The average number needed to treat for 5 years to prevent one major adverse CV event was 16 patients. Qualitatively similar effects are evident when analyzing the component endpoints of all-cause mortality (HR 0.88; 95% CI 0.65-1.01) and fatal CHD events (HR 0.59; 95% CI 0.48-0.97), although pooled analysis of death alone failed to achieve statistical significance (see **Table 15-6**).

Meta-analyses of Statin Efficacy Among Diabetes Mellitus Patients

In the Cholesterol Treatment Trialists' Collaboration (CTT) prospective meta-analysis of data from 90,056 participants in 14 statin randomized controlled trials (among whom 21% had DM), statin therapy safely reduced 5-year incidence of major adverse coronary events (MACEs) and coronary

TABLE 15-6 Statins Effects on Lipids and apo B and Primary Outcome (Ranked by Low-Density Lipoprotein Cholesterol [LDL-C] Reduction) in Diabetes Trials and Substudies

ACRONYMS	ACTIVE ARM (n)	CONTROL ARM (n)	FOLLOW-UP (yr)	THERAPY	DOSAGE (mg)	CONTROL	LDL-C	HDL-C	NON–HDL-C	TG	apo B	DELTA LDL-C (mg)	DELTA LDL-C (%)	EVENTS ACTIVE ARM (n)	ANNUAL RATE (%)	EVENTS CONTROL (n)	ANNUAL RATE (%)	HR	95% CI	P	ARR (%)	RRR (%)	5-YEAR NNT
GREACE (DSS)	161	152	3	atorva	23.7	Usual care	97	43	123	142		−92	−49	20	4.1	46	10.1	0.41		<.0001	17.8	59	3
4S (DSS)	105	97	5.4	simva	20-40	Placebo	119	46	143	134		−67	−36	15	2.6	24	4.6	0.58		.087	10.5	42.3	
4D	619	636	4	atorva	20	Placebo	72					−53	−42	226	9.1	243	9.6	0.96	0.77-1.1	.37	1.7	4.4	
SPARCL (DSS)	395	399	4.9	atorva	80	Placebo	81	48	106	137		−50	−38										
ASCOT-LLA (DDS)	1258	1274	3.3	atorva	10	Placebo	81	47	108	136		−47	−37	116	2.8	151	3.6	0.78	0.61-0.98	.036	2.6	22.2	25
CARDS	1428	1410	3.9	atorva	10	Placebo	70	55	99	140	90	−47	−40	83	1.5	127	2.3	0.65	0.48-0.83	.001	3.2	35.5	24
PROVE IT–TIMI 22 (DSS)	499	479	2	atorva	80	prava 40	57					−44	−44	142	14.2	152	15.9	0.88		0.28	3.3	10.3	
AURORA (DSS)	388	343	2.8	rosuva	10	Placebo	54	45	83	146		−43	−39	85	7.8	104	10.8	0.72	0.51-0.90	0.008	8.4	27.7	7
CARE (DSS)	282	304	5	prava	40	Placebo	96	40	130	143		−40	−27	81	5.7	112	7.4	0.78		<.0001	8.1	22	12
HPS—MRC/BHF (DSS)	2978	2985	4.8	simva	40	Placebo	89	41	136	177	84	−35	−28	601	4.2	748	5.2	0.81	0.19-0.30	<.0001	4.9	19.5	20
ASPEN	1211	1199	4	atorva	10	Placebo	79	48	108	141		−34	−30	166	3.4	180	3.8	0.91	0.73-1.12	.341	1.3	8.7	
TNT (DSS)	753	748	4.9	atorva	80	atorva 10	77	45	106	145		−19	−20	103	2.8	135	3.7	0.76	0.58-0.97	.026	4.4	24.2	22
Total (n = 20,103)	10,077	10,026												1638		2022							
Mean			4.0				81	46	114	144		−48	−36		5.3		7.0	0.76			6.0	25	16

All lipids measurements correspond to on-treatment values (in mg/dL).
See **Table 15-1** for acronyms definition and **Table 15-2** for primary outcomes description.
ARR = Absolute risk reduction; atorva = atorvastatin; CI = confidence interval; NNT = number needed to treat; prava = pravastatin; rosuva = rosuvastatin; RRR = relative risk reduction; simva = simvastatin.

revascularization by approximately 20% per 40 mg/dL (1.0 mmol/L) LDL-C reduction, and largely independent of baseline LDL-C.[109] Other meta-analyses have confirmed these observations that statins effectively reduce CHD outcomes with or without DM in both primary and secondary prevention populations,[110–112] including meta-analyses focused only on statin efficacy among DM participants.[111]

Patients with DM could possibly benefit even more from the cardioprotective effects of statins than those without DM,[110] and the authors of the CTT meta-analysis of 18,686 diabetic patients from 14 randomized controlled trials went as far as to recommend considering statin therapy for all patients with DM and elevated risk for incident CV events, based on the 21% proportional reduction in MACE for every 40 mg/dL (1.0 mmol/L) LDL-C reduction.[111] However, this may overestimate statin efficacy to some degree because of the exclusion from the analyses of data from the ASPEN trial, which was a DM-specific trial of atorvastatin that failed to demonstrate statistically significant differences in CV outcomes.[18]

Statin Use, Glucose Homeostasis, and New-Onset Diabetes

Much has been discussed with regard to cholesterol metabolism, use of statins, and drug-induced pancreatic beta cell dysfunction,[113–121] with a modest diabetogenic action of statins increasingly considered an infrequent, likely dose-dependent side effect affecting most of the drugs within the class. Incident diabetes cases observed in randomized controlled statin trials have been reported and included in meta-analysis of data from eight landmark trials (A to Z; ASCOT-LLA; GREACE; HPS—MRC/BHF; IDEAL; JUPITER; SPARCL; TNT).* On a population basis, statins may cause marginal increases in blood glucose—both fasting and postprandial—in predisposed individuals. This translates into a slight increase in glycated hemoglobin A1c (HbA1c) and for patients with baseline values just below diagnostic thresholds leads to a small excess in incident DM cases for statin versus control patients. In most patients with small increases in HbA1c, this observation is of uncertain clinical relevance. For patients already diagnosed with DM, subtle deterioration of glycemic control and/or a rise in HbA1c, if it occurs, appear equally modest, even verging on the trivial when put into perspective with the cumulative rise in blood glucose over years associated with the relentless loss of residual beta cell function.

Because major randomized controlled trials investigate very large numbers of patients, such an effect, however small, may produce highly significant statistics, despite limited clinical relevance. Indeed, the ratio between number needed to treat (to avoid occurrence of one major CHD event) versus number needed to harm (i.e., new-onset diabetes or glucose control worsening in patients with already known T2DM) remains unquestionably in favor of using statins to lower LDL-C, whatever a patient's glucose homeostasis at the time of statin initiation,[120] an opinion underpinned by the recent American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) cholesterol treatment guidelines.[122,150]

Ezetimibe

Ezetimibe is a selective blocker of intestinal cholesterol absorption, which binds to Niemann-Pick C1-like 1 (NPC1L1) receptors in the gut (**Fig. 15-4**). Whereas ezetimibe monotherapy moderately lowers LDL-C (<20%), it markedly reduces it when coadministered with a statin. Ezetimibe counteracts, in a complementary manner, the intestinal absorption of cholesterol that is often upregulated by statins; this upregulation reduces the LDL-C–lowering effectiveness of statins in patients with high intestinal ability to reabsorb cholesterol from the intestinal lumen whenever hepatic synthesis is constrained by statin inhibition of HMG-CoA reductase. Combination therapy with statin plus ezetimibe may represent an alternative approach to further reduce LDL-C when statin monotherapy is insufficient to lower LDL-C to target levels, as confirmed in a lipid-lowering efficacy meta-analysis.[123]

With regard to CHD outcomes data, the clinical evidence for benefit of ezetimibe is currently limited. In the SHARP trial, 9270 patients with advanced renal disease (among whom 23% had diabetes at inclusion) were randomly assigned to treatment with simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo with mean trial follow-up of 4.9 years. There was a significant reduction in major atherosclerotic events (coronary death, MI, ischemic stroke, or any revascularization procedure) in the simvastatin-ezetimibe group versus placebo, with an HR of 0.84 (CI 0.74-0.94; $P=0.0021$) with a number needed to treat for 5 years of 47 patients. In SHARP, the treatment response in the subgroup of patients with DM did not differ from the findings of the overall trial.[70] However, it remains unclear as to what extent each of the lipid-lowering drugs that were combined contributed to the results.

IMPROVE-IT is ongoing and is comparing the effects of a combination of simvastatin (40 mg)+ezetimibe (10 mg) daily versus simvastatin (40 mg) alone in 18,000 very high-risk patients with ACS, among whom a large subgroup (22%) had DM at enrollment.[45]

The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) investigated, in an open-label design, the effect of ezetimibe (10 mg) versus extended-release (ER) niacin (2000 mg) daily in 315 patients with CHD or CHD equivalent (among whom 40% had DM at inclusion), given on top of background statin therapy. The trial was terminated early on the basis of a prespecified interim analysis showing superiority of ER niacin over ezetimibe on carotid artery intima-media thickness regression ($P<.001$).[124] It should be noted that the study design, by isolating niacin's additional actions on HDL-C and TGs from its LDL-C–lowering effects, could have disadvantaged detection of a beneficial effect of long-term ezetimibe therapy. Thus, part of atherosclerosis regression in the ER niacin arm could theoretically be ascribed to changes in components of atherogenic dyslipidemia. Given the high proportion of patients with DM in ARBITER 6-HALTS trial, a specific analysis of the respective benefits of these two lipid-lowering approaches in these patients would be of great interest. At the time of writing this chapter, no definitive data either support or call into question the effectiveness of ezetimibe, alone or in combination with statins, to reduce CHD events in patients with DM.

Drugs Targeting High-Density Lipoprotein Cholesterol

Given the epidemiologic evidence of a link between a low HDL-C level (or a decreased number of HDL) and increased CHD risk in nondiabetic and diabetic populations, it was

*References 5, 16, 17, 36, 40, 44, 71, 75, 119-121.

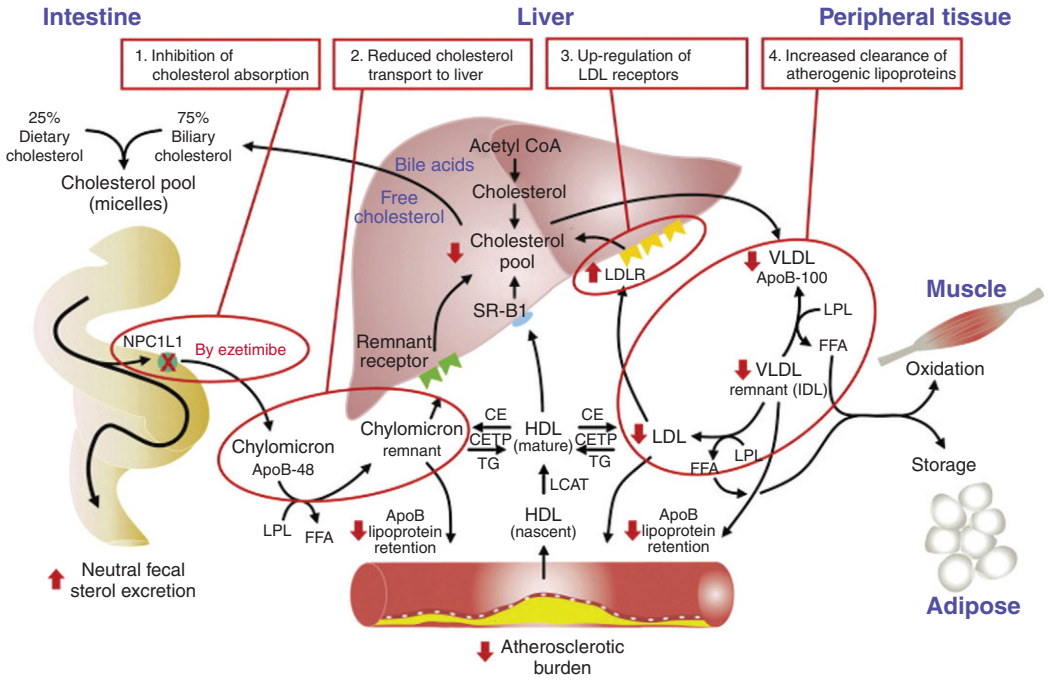


FIGURE 15-4 Ezetimibe mechanism of action. Mechanism of action for reduction of atherogenic ApoB-containing lipoproteins by ezetimibe, and potential effects on atherosclerotic burden. ApoB = Apolipoprotein B; CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; FFA = free fatty acid; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; LPL = lipoprotein lipase; NPC1L1 = Niemann-Pick C1 Like 1 sterol transporter; SR-B1 = scavenger receptor type B1; TG = triglyceride; VLDL = very low-density lipoprotein. *(From Davis HR, Lowe RS, Neff DR.* Atherosclerosis *215: 266-278, 2011.)*

logical to target HDL-C levels and/or the number of HDL particles as lipid-related modifiable CV risk factors in DM patients. However, several classes of drugs that alter HDL-C levels and/or function have failed to yield significant improvements in CV risk, as described in the following section. And although treatment with fibric acid derivatives (fibrates) does have a modest effect on raising HDL-C, their principal mechanism of action modulates circulating TG levels, and therefore this class of medications will be reviewed in the following section on TGs.

Niacin

Niacin (nicotinic acid) is a broad-spectrum lipid-altering drug with multiple effects on lipids and lipoproteins. In hepatocytes, niacin inhibits microsomal diacylglycerol acyltransferase 2 (DGAT2), resulting in decreased TG synthesis, lowered VLDL assembly, and increased intrahepatic apo B degradation (**Fig. 15-5**). Niacin impairs apo B and VLDL secretion; decreases TG, apo B, non–HDL-C, LDL-C, and lipoprotein(a) levels; and also reduces the number of VLDL (especially TG-rich VLDL) and small dense LDL-Ps. Niacin

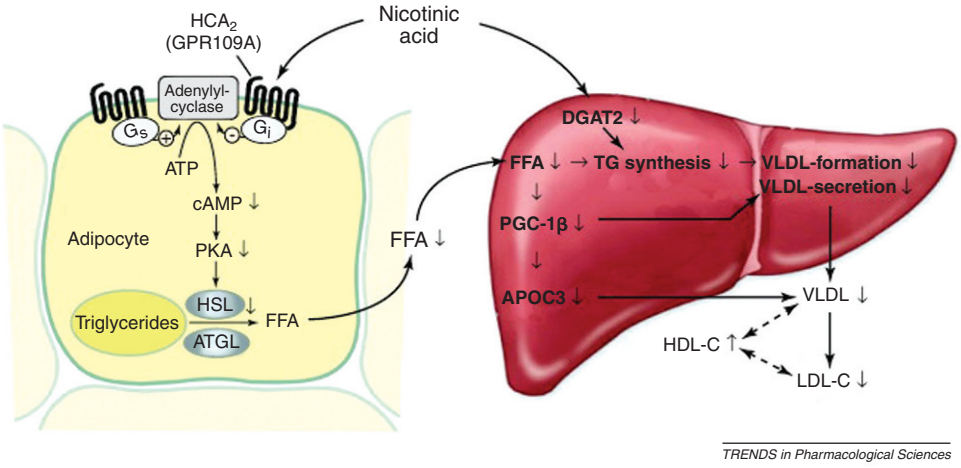


FIGURE 15-5 Niacin (nicotinic acid) mechanisms of action. Potential mechanisms underlying the antidyslipidemic effects of nicotinic acid. Activation of the nicotinic acid receptor HCA_2 on adipocytes via the heterotrimeric G protein, Gi, leads to inhibition of adenylyl cyclase. Decreased cAMP levels via reduced activation of protein kinase A (PKA) results in an inhibition of lipolysis. Owing to this antilipolytic effect, free fatty acid (FFA) plasma levels drop, and triglyceride (TG) synthesis in the liver is reduced resulting in decreased very-low-density lipoprotein (VLDL) formation. A reduced supply of FFAs to the liver also suppresses hepatic expression of PPARγ coactivator-1β (PGC-1β) and of apolipoprotein C3 (APOC3). Decreased PGC-1β expression reduces VLDL formation and secretion. Under in vitro conditions, nicotinic acid has also been shown to inhibit triglyceride synthesis by a direct inhibitory effect on diacylglycerol acyltransferase 2 (DGAT2). The reduced expression of APOC3 may contribute to the decrease in VLDL levels by increasing VLDL turnover. Reduced VLDL levels result in reduced LDL cholesterol levels. How HDL cholesterol levels increase in unclear. This effect may be due to decreased expression of the cholesterol ester transfer protein (CETP) or the decreased exchange of triglycerides from VLDL and LDL particles against cholesterol esters of HDL particles. ATGL = adipocyte triglyceride lipase; HSL = hormone sensitive lipase. For details, see text. *(From Lukasova M, Hanson J, Tunaru S, et al. Nicotonic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials.* Trends Pharmacol Sci *32:700-707, 2011.)*



also decreases liver fractional catabolism of apo A-I–HDL, increasing the levels of apo A-I and HDL-C, and raising type 2 HDL number. In adipose tissue, niacin modulates TG lipolysis and fatty acid mobilization. The range of niacin's lipid effects theoretically means that it could be a choice drug to treat LDL-C and/or atherogenic dyslipidemia in DM patients with low HDL-C, elevated small dense LDL particles, and/or hypertriglyceridemia.

Niacin use, especially at the beginning of treatment, often causes vasocutaneous flushing, whereas chronic niacin intake may impair insulin sensitivity, causing DM in some patients and, in those with DM, adversely influencing glucose control.[125] To mitigate flushing, ER formulations of niacin or a fixed-dose combination of niacin with laropiprant, an antiflush pharmacologic agent, have been introduced. However, recent large clinical trials of these formulations have failed to demonstrate reduction in CV risk, with the clinical benefit suggested in earlier studies challenged by small sample sizes and high dropout rates as a result of flushing.

Niacin Clinical Trial Results

In the Coronary Drug Project (CDP), a trial comprising 3908 men with a history of MI with mean study follow-up of 6.2 years, there was a significant reduction in the primary outcome (all-cause mortality) with niacin (3000 mg) daily versus placebo. Of note, the beneficial effect became evident only years after the end of the study. Whereas the prevalence of diabetes at enrollment was not reported, the benefits of niacin were observed irrespective of the presence of impaired fasting glucose, DM, and/or a metabolic syndrome at inclusion.[126] In the Stockholm Ischaemic Heart Disease study, conducted in 555 patients with a history of MI over a mean follow-up of 5 years, there was a significant reduction in total mortality (HR 0.74; $P=0.05$) and CHD mortality (HR 0.64; $P<.01$) with niacin (3000 mg) plus clofibrate (2000 mg) daily versus placebo.[127] In the HDL-Atherosclerosis Treatment Study (HATS), conducted in 160 patients with CHD, low HDL-C, and normal LDL-C (among whom 16% had DM at inclusion) over a mean follow-up of 3 years, the risk of the composite primary endpoint (CHD death, MI, stroke, revascularization for ischemic symptoms) was 90% lower ($P=0.03$) with a combination of niacin (2000 to 4000 mg) plus simvastatin (10 to 20 mg) daily versus placebo.[128]

As summarized earlier, the ARBITER 6-HALTS trial compared the addition of ezetimibe (10 mg) versus ER niacin (2000 mg) daily in 315 patients (of whom 40% had diabetes) with CHD or CHD equivalent, given on top of background statin therapy. The trial was terminated early based on a prespecified interim analysis showing superiority of ER niacin over ezetimibe on carotid artery intima-media thickness regression ($P<.001$).[124]

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was conducted in 3414 patients with prior CVD (among whom 34% had DM and 80% a metabolic syndrome at inclusion). The trial was interrupted early because of futility after a mean follow-up of 3 years at the time of termination; there was no benefit of ER niacin (1500 to 2000 mg) daily versus placebo, given in addition to standardized background LDL-C–lowering therapy with simvastatin 40 to 80 mg plus or minus ezetimibe 10 mg daily to maintain LDL-C levels at 40 to 80 mg/dL (1.03 to 2.07 mmol/L). Whereas the primary composite outcome of CHD death, MI, ACS, ischemic stroke, and/or symptom-driven revascularization was not reduced (HR 1.02; CI 0.87-1.21; $P=0.80$), broad-spectrum improvements in lipids and lipoproteins—increased HDL-C, decreased TG, and lowered LDL-C—were recorded after addition of ER niacin. Of interest, there were no significant interactions with respect to primary endpoint occurrence according to presence or absence of DM at inclusion. However, a post hoc analysis found a 36% relative reduction of the primary outcome ($P=0.032$) in a subgroup of 439 patients with marked atherogenic dyslipidemia (defined as TGs $\geq$200 mg/dL [$\geq$2.3 mmol/L] and HDL-C <32 mg/dL [<0.83 mmol/L]).[129,130]

In HPS2-THRIVE, the risk of the composite primary endpoint (nonfatal MI or CHD death; stroke or [non]coronary revascularization) was not significantly different among 25,673 patients with either MI or cerebrovascular disease or peripheral arterial disease, or with DM plus CHD (the latter amounting to 32% of enrolled patients) randomized to ER niacin + laropiprant (2000 mg + 40 mg) or placebo over a median follow-up of 3.9 years, given in addition to standardized background LDL-C–lowering therapy (simvastatin 40 mg $\pm$ ezetimibe 10 mg daily) to maintain a total cholesterol target of 135 mg/dL (3.5 mmol/L).[42,131] There were, on the other hand, significant increases with ER niacin + laropiprant in diabetic complications (HR 1.55; CI 1.34-1.78; $P<0.0001$); new-onset DM (HR 1.27; CI 1.14-1.41; $P<0.0001$); and other side effects (infection; gastrointestinal effects; musculoskeletal, bleeding, and skin adverse events).

In a systematic meta-regression review of 9959 patients treated with niacin to reduce CVD, a significant reduction in incidence of the composite endpoints of any CV events was reported (HR 0.75; CI 0.59-0.96; $P=0.02$), irrespective of on-treatment HDL-C changes.[132] In the setting of subpopulations with DM, as for ezetimibe, a formal demonstration of the effectiveness of niacin, ER niacin, or niacin/laropiprant, alone or in combination with statins, to reduce CHD events is not currently available. Based on the negative results of these most recent large-scale clinical outcomes trials of niacin preparations, in 2013 the European Medicines Agency (EMA) recommended that the marketing, supply, and authorizations of three identical niacin + laropiprant products for the treatment of adults with dyslipidemia be suspended across the European Union; none of the formulations had been approved for use in the United States.

Cholesteryl Ester Transfer Protein Inhibition

Cholesteryl ester transfer protein (CETP) mediates intravascular transfer and exchange of cholesteryl ester and TG between TG-rich lipoproteins (and their remnants) and HDL. An antiatherogenic potential has been suggested on the basis of a considerable rise in HDL-C, combined with a substantial decrease in LDL-C, lipoprotein(a), and apo B levels after pharmacologic inhibition of CETP. Clinical results for the first two CETP inhibitors were, however, problematic. Torcetrapib development was stopped because of higher rates of CV events and mortality in the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial comprising 15,067 patients, of whom 44% had DM at inclusion. Development of the CETP inhibitor dalcetrapib was also discontinued because of ineffectiveness, based on data from the dal-OUTCOMES trial in 15,871 ACS patients, 25% of whom had DM at baseline.

Regarding other CETP inhibitors under study, there has not been any general safety issue reported in ongoing prospective outcomes studies so far. REVEAL and ACCELERATE (A Study of Evacetrapib in High-Risk Vascular Disease) are currently evaluating whether the broad range of lipid modifications induced by CETP inhibition translate into CV risk reduction in patients with a past MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, and/or DM with evidence of symptomatic CHD (REVEAL), and in patients with high-risk vascular disease (past ACS, cerebrovascular atherosclerotic disease, peripheral arterial disease, and/or DM with coronary artery disease [ACCELERATE]).[67,133–138]

Drugs Targeting Triglycerides

Because pharmacologic lowering of LDL-C by statins (alone or combined with ezetimibe) has minimal effects on HDL-C and TG levels, atherogenic dyslipidemia remains frequent among patients treated for elevated LDL-C, even when LDL-C targets are achieved. Among the currently available medications targeting TG and atherogenic dyslipidemia (see **Chapter 10**), fibrates, niacin, and omega-3 fatty acids are known to improve one or more lipid abnormalities characteristic of DM, including atherogenic dyslipidemia components.

Fibric Acid Derivatives (Fibrates)

Fibrates are pharmacologic agonists of PPAR-α, which are nuclear receptors that coordinately regulate gene transcription. Activated PPAR-α regulates genes involved in lipoprotein metabolism, including apo A-I and apo A-II (HDL particle formation); lipoprotein lipase (TG-rich particles lipolysis); apo C-III (decreasing TG-rich particle numbers and small dense LDL particles); apo A-V (decreasing TG levels); adenosine triphosphate (ATP)–binding cassette transporter A1 (ABCA1) (promoting cholesterol efflux and reverse cholesterol transport); scavenger receptor B1 (HDL capture and catabolism); and transrepression of nuclear factor κB and activator protein 1 transcription factors (anti-inflammatory and parietal vascular protection) (**Fig. 15-6**). Reported effects of fibrates on lipids and lipoproteins among DM patients participating in clinical outcomes trials include mean on-treatment TG levels of 147 (SD 29) mg/dL (1.7 [SD 0.3] mmol/L), with absolute and relative mean reductions of 39 mg/dL (0.4 mmol/L) and 19%, respectively. Average on-treatment LDL-C was 120 (37) mg/dL (3.1 [1.0] mmol/L); HDL-C 41 [5] mg/dL (1.1 [0.1] mmol/L); non–HDL-C 152 (43) mg/dL (3.9 [1.1] mmol/L; and apo B 108 (28) mg/dL.*

Most clinical trials of fibrates have included patients without and with DM; the DM subsets were most often too small for meaningful conclusions to be drawn about efficacy specifically in patients with DM.† Two trials have evaluated the effects of fenofibrate specifically in high-risk DM populations. The FIELD trial investigated the effects of fenofibrate (200 mg/day) versus placebo in 9795 patients with T2DM with or at risk for CVD, with a primary composite outcome of CHD death or nonfatal MI. Eligibility criteria also included total cholesterol (TC) 116 to 251 mg/dL (3.0 to 6.5 mmol/L) and either TC/HDL-C ≥4 or TGs 89 to 443 mg/dL (1.0 to 5.0 mmol/L). Over a mean follow-up of 5 years with 544 primary endpoint events occurring, differences in the primary outcome were not statistically different (HR 0.89; CI 0.75-1.05).[32–34] The ACCORD-Lipid trial investigated the effects of fenofibrate (160 mg/day) versus placebo, each added to background simvastatin therapy, in 5518 patients with DM and high CV risk with a primary composite outcome of CV death, MI, or stroke. Over a mean follow-up of 4.7 years with 601 primary outcome events for analysis, there was no significant difference between the groups (HR 0.92; 95% CI 0.79-1.08).[6–8]

Although fenofibrate therapy was ineffective to reduce risk for the primary composite outcome in the overall cohort, analyses of the prespecified subgroup (17%) of patients with atherogenic dyslipidemia at inclusion (defined as fasting TGs >204 mg/dL [2.3 mmol/L] and HDL-C <34 mg/dL [<0.9 mmol/L]) yielded a statistically significant 31% reduction ($P < .05$). The implications of ACCORD-Lipid are threefold: (1) T2DM patients with atherogenic dyslipidemia have a 70% increase in relative risk for CHD compared with those without atherogenic dyslipidemia, even when LDL-C is controlled with simvastatin; (2) addition of fenofibrate to simvastatin appears to reduce CV events, although with noted limitations of subset analyses in an overall neutral trial; and (3) such dual therapy was well tolerated.

General Limitations of the Available Fibrate Data

The most significant limitation of the totality of the fibrate data is the failure to limit the evaluation to patients with atherogenic dyslipidemia, with trials evaluating broad CV risk cohorts or cohorts with DM with or without atherogenic dyslipidemia. This limitation is highlighted by the biologic plausibility of the atherogenic influence of high TGs combined with low HDL-C; the known mechanism of action of the fibrates; and subanalyses across multiple trials consistently demonstrating efficacy of fibrates in patients with the combination of high TGs and low HDL-C. Thus, the fragmented amount of direct clinical evidence results from a lack of randomized clinical trials, on a large scale, comparing fibrates and statins head to head, or investigating the additional effect of fibrates (versus placebo) in combination therapy with statins in long-term studies that would have included only patients with high TGs, or atherogenic dyslipidemia, with and without DM. For these reasons, until further data come available, it is most appropriate to interpret the evidence to date regarding fibrate effects on CHD outcomes in light of the following: lipid characteristics at entry, including hypercholesterolemia versus non-LDL dyslipidemia and average TG levels; concomitant treatment with statins at entry, or statin admission during follow-up; and CV risk of enrollees at baseline, including that related to the proportion of patients with DM, the latter usually with T2DM at presentation, comorbid with atherogenic dyslipidemia and/or hypertriglyceridemia.

Omega-3 Fatty Acids

Oral supplementation with omega-3 (n-3) fatty acids (marine-derived eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] and plant-derived alpha-linolenic acid [ALA]) decreases hypertriglyceridemia, inhibits platelet aggregation, improves plaque stability and endothelial function, and prevents certain arrhythmias. It is on the basis of these observations that large clinical outcomes trials have

*References 6-8, 28-30, 32-34, 39, 69, 81.
†References 22, 23, 38, 39, 48, 49, 79-82.

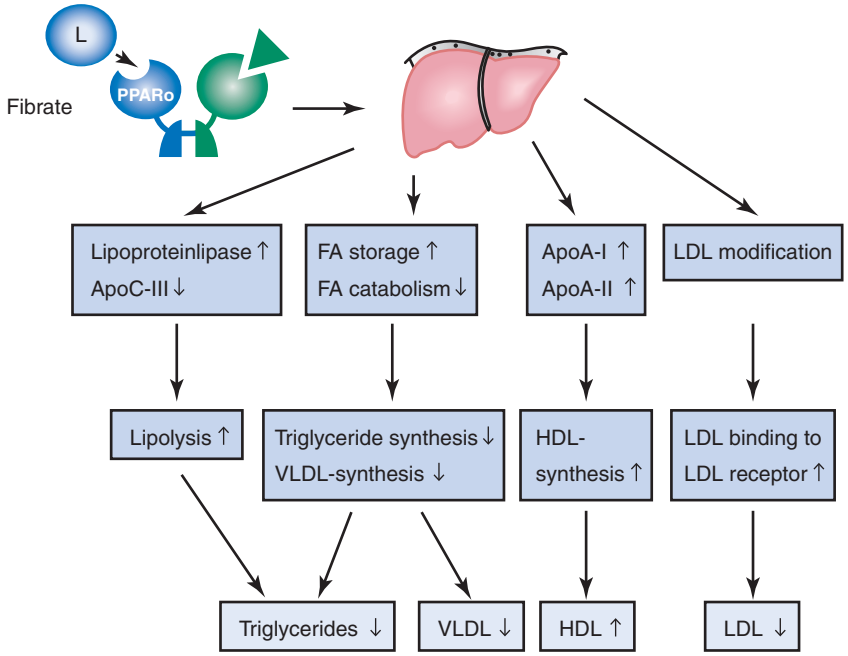


FIGURE 15-6 Fibrates mechanisms of action.

been conducted to evaluate the potential benefits of these supplements on CV events and death.

In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), 18,645 patients with hypercholesterolemia (among whom 16% had DM at inclusion) were given EPA (1.8 g/day) plus statin versus statin alone during a mean follow-up of 4.6 years. There was a significant reduction in the primary outcome of developing any MACE (HR 0.81; CI 0.69-0.95; $P=0.011$). In the small subgroup of patients with atherogenic dyslipidemia at enrollment (TGs ≥150 mg/dL (≥1.7 mmol/L) and HDL-C below 40 mg/dL (<1.0 mmol/L; 5% of the total study population), n-3 supplementation was associated with a significant 53% RRR.[143,144] Similarly, in a subanalysis stratified by glucose status within the first 6 months of the trial, 4565 patients with DM or impaired fasting glucose had a 22% ($P=0.048$) reduction in the primary composite event with EPA treatment.[145]

In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, 12,536 patients with dysglycemia (impaired fasting glucose or glucose intolerance [18%] or diabetes [82%]), among whom 59% had a history of MI, stroke, or revascularization were randomized to EPA (465 mg) and DHA (375 mg) daily versus placebo, with the primary outcome of CV death. Over a median 6.2 years, EPA or DHA had no significant effect on the primary outcome that occurred in 1155 patients (HR 1.01; 0.87-1.17; $P=0.93$).[146]

A meta-analysis of 20 trials in 68,680 patients who received supplementation of, on average, 1.51 g of omega fatty acids per day failed to demonstrate a decrease in total mortality, cardiac death, sudden death, MI, or stroke.[147] All in all, the benefits of supplementation with omega-3 fatty acids are discordant according to studies, and generally disappointing in recent clinical trials and meta-analyses. Although large numbers of patients have been included in completed trials of n-3 supplementation, meta-analysis of efficacy has not been reported.

Other Trials with Lipid Intervention in Diabetes Mellitus Patients

In the PROACTIVE randomized placebo-controlled CV outcomes trial, addition of pioglitazone, a glucose-lowering PPAR-γ agonist that has some degree of PPAR-α agonism, versus placebo resulted in complementary improvement in lipids and lipoproteins as a result of pioglitazone's pleiotropic effects on lipid metabolism and fatty acid oxidation. In PROACTIVE, patients with T2DM patients and prevalent CVD were randomized to receive pioglitazone (target dose 45 mg daily) versus placebo. The incidence of the primary composite outcome (death, MI, stroke, unstable angina, coronary or peripheral revascularization, amputation) was not statistically different between the groups (HR 0.90; CI 0.80-1.02), but the prioritized secondary outcome of death, MI, or stroke did demonstrate superiority of pioglitazone (HR 0.84; CI 0.72-0.98) with an absolute risk reduction of 3.4%, a RRR of 16%, and a 3-year number needed to treat of 29 patients.[61,62] It remains unclear to what extend the lipid-modifying properties of pioglitazone have influenced these results.

In the intensified multifactorial Steno-2 intervention study, which combined lipid-lowering agents (statin and/or fibrate), renin-angiotensin system blockers, aspirin, and tight glucose regulation in patients with T2DM and microalbuminuria, a significant and pronounced reduction in all-cause mortality was observed (HR 0.60; CI 0.32-0.89; $P=0.02$), amounting to an absolute risk reduction of 20%; a RRR of 40%; and a number needed to treat for 5 years of 13 patients.[73] One must nevertheless acknowledge the limited statistical precision of these estimates, as the overall trial randomized only 160 participants, who experienced a limited total number of incident events. Furthermore, it is not possible, because of the multifactorial design, to quantify the beneficial component related to lowering of LDL-C or other lipids from those related to improvement in nonlipid risk factors.

The Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care

(ADDITION-Europe) investigated 3057 newly diagnosed patients with T2DM randomized to either routine care or intensive treatment of CV multiple risk factors. Despite improvement in cholesterol levels, blood pressure, and HbA1c, there was no significant reduction in CV events (HR 0.83; CI 0.65-1.05) or total mortality (HR 0.91; 0.69-1.21).[148]

CLINICAL PRACTICE GUIDELINES FOR LIPID-LOWERING THERAPIES

Most published guidelines for lipid management advocate intensive lowering of elevated LDL-C in adult patients with hypercholesterolemia, based on therapeutic lifestyle interventions and with statin therapy as the primary pharmacologic intervention. Because of their heightened CV risk, patients with DM are a choice group to benefit from widespread statin use in primary or secondary CV prevention, irrespective of baseline LDL-C levels. Thus, DM patients without overt CVD are often considered as having CHD risk equivalency, and on that basis the LDL-C levels to trigger statin initiation and commensurate LDL-C targets are often lower than those for nondiabetic patients.[99,149,151–155] All in all, most guidelines and consensus statements from diabetes or cardiology scientific societies regarding management of dyslipidemia for patients with DM advocate aggressive lowering of LDL-C. In addition to therapeutic lifestyle changes, statin therapy is considered the mainstay of dyslipidemia management (ADA; European Association for the Study of Diabetes [EASD]; European Society of Cardiology [ESC]; European Atherosclerosis Society [EAS]; National Cholesterol Education Program; Canadian Cardiovascular Society; ACC).[98–108,150]

2011 European Society of Cardiology and European Atherosclerosis Society Guidelines for the Management of Dyslipidemias

The 2011 ESC/EAS guidelines for the management of dyslipidemias endorse the use of the SCORE risk estimating equation to categorize patients into risk categories, on which recommendations for lipid management are based. Four categories based on total CV risk are listed; patients with DM are, in general, at very high or high risk, especially those with T2DM.[98]

- *Very high risk:* patients with documented CV disease, previous MI, ACS, coronary revascularization and other arterial revascularization procedures, ischemic stroke, or peripheral arterial disease; patients with DM plus target organ damage (e.g., microalbuminuria); patients with moderate to severe chronic kidney disease; and patients whose calculated 10-year SCORE risk for fatal CV disease is 10% or higher
- *High risk:* patients with markedly elevated single risk factors (e.g., familial dyslipidemias) and patients with 10-year SCORE risk of 5% to 10%
- *Moderate risk:* patients with 10-year SCORE risk of 1% to 5%, with risk modulated according to family history of premature CAD, abdominal obesity, physical activity, HDL-C, TGs, C-reactive protein, lipoprotein(a), fibrinogen, homocysteine, apo B, and social class
- *Low risk:* individuals with 10-year SCORE risk below 1%

In this context, all patients at very high or high risk should be treated with medical therapy in addition to professional advice on lifestyle changes, whereas those at moderate risk should receive lifestyle advice with or without lipid-modifying medication(s), and low-risk patients should be treated with lifestyle advice alone.[98] The guidelines recommend pretreatment lipid profile assessment with LDL-C as the primary focus; TGs and HDL-C may be considered to complement risk assessment and to refine therapeutic choice; and apo B measurement is recommended for better risk characterization of patients with DM and/or the metabolic syndrome. LDL-C is the paramount treatment target, whereas total cholesterol is an alternative treatment target if other analyses are unavailable. TGs should be monitored during treatment of patients with hypertriglyceridemia, but measurement of on-treatment HDL-C is not recommended as a therapeutic target, nor are calculations of on-treatment apo B/apo A-I and non–HDL-C/HDL-C ratios. Non–HDL-C is a secondary target for patients with DM and/or the metabolic syndrome; apo B is also a secondary treatment target.[98] In all T2DM patients, bringing LDL-C below 100 mg/dL (<2.6 mmol/L) is the primary target. Non–HDL-C below 130 mg/dL (<3.4 mmol/L) and overall apo B below 100 mg/dL are secondary targets (class I recommendation; level of evidence B). In patients with T2DM and CHD or CKD, and in those without CHD older than 40 years with one or more other CHD risk factors or markers of target organ damage, the primary goal is to lower LDL-C to below 70 mg/dL (<1.8 mmol/L), and the secondary goals are to bring non–HDL-C to below 100 mg/dL (<2.6 mmol/L) and apo B to below 80 mg/dL (class I recommendation; level of evidence B). In all patients with T1DM and in the presence of microalbuminuria and renal disease, LDL-C lowering by at least 30%, with statins as first choice and eventually with a drug combination, is recommended irrespective of baseline LDL-C (class I recommendation; level of evidence C).[98]

2013 European Society of Cardiology and European Association for the Study of Diabetes Guidelines on Diabetes, Prediabetes, and Cardiovascular Diseases

The 2013 ESC guidelines on diabetes, prediabetes, and CVD developed in collaboration with the EASD recommend classification of patients with DM as being at very high risk or high risk for CVD depending on the presence of concomitant risk factor and target organ damage. They do not recommend assessment of CVD risk in DM patients based on scores developed for the general population. Estimation of urinary albumin excretion rate is indicated when risk stratification of DM patients is performed, whereas screening for silent myocardial ischemia may be considered in selected high-risk DM patients.[150]

Statin therapy is recommended for patients with T1DM and T2DM at very high risk (diabetes with at least an additional cardiovascular risk factor or target organ damage), with an LDL-C target of below 70 mg/dL (<1.8 mmol/L), or at least a 50% reduction of LDL-C when this target cannot be attained. Treatment with a statin is also recommended for patients with T2DM at high risk, with an LDL-C target of below 100 mg/dL (<2.6 mmol/L). For T1DM patients at high risk, statin use may also be considered irrespective of baseline LDL-C. A secondary goal of on-treatment non–HDL-C below 100 mg/dL (<2.6 mmol/L) may be considered in patients with DM at very high risk, and of below 130 mg/dL (<3.4 mmol/L) in patients at high risk. In addition, intensification of statin therapy should be considered before combination therapy with

ezetimibe. Finally, the use of drugs that increase HDL-C levels to prevent CVD in T2DM is not recommended.[150] Recommendations from other major scientific associations are often consensual with respect to primary and secondary lipid and lipoprotein targets to be achieved through therapeutic lifestyle changes and lipid-lowering drugs, alone or in combination in patients with DM, in primary prevention or secondary prevention.[98–108]

2013 American College of Cardiology and American Heart Association Guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: Global Risk Assessment for Primary Prevention

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: Global Risk Assessment for Primary Prevention recommends the use of the Pooled Cohort Equations to estimate 10-year atherosclerotic CVD risk in both white and black men and women and to more accurately identify higher-risk individuals for statin therapy, focusing this treatment on those most likely to benefit.[122] This guideline proposes a paradigmatic revision of the management of hypercholesterolemia, which is the subject of ongoing debate. Thus, for secondary CV prevention (with or without DM), high-intensity statin therapy (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg/day) is recommended to lower LDL-C by 50% or more on average, with combination therapy to be considered if a 50% reduction is not achieved. For patients 40 to 75 years old with T1DM or T2DM in primary prevention whose LDL-C is 70 to 189 mg/dL (1.8 to 4.9 mmol/L), absolute 10-year risk of atherosclerotic CVD should be computed using the Pooled Cohort Equations. If the calculated risk is below 7.5%, moderate-intensity statin therapy is advocated (atorvastatin 10 to 20 mg; rosuvastatin 5 to 10 mg; simvastatin 20 to 40 mg; pravastatin 40 to 80 mg; lovastatin 40 mg; ER fluvastatin 80 mg; fluvastatin 2×40 mg; pitavastatin 2 to 4 mg—all daily doses); if calculated absolute risk is 7.5% or higher, high-intensity statin therapy (as defined earlier) is recommended.[122]

Reconciling Discordance in the Guidelines

Simultaneous achievement of several therapeutic targets inevitably leads to consider the pros and cons of two escalation approaches: one that involves using several lipid-lowering medications with complementary mechanisms of action, and another that advocates dose-titration of monotherapy. With regard to multiple lipid target achievements in DM patients, the frequent joint presence of atherogenic dyslipidemia is associated with lower success in achieving recommended targets for managing hypercholesterolemia—namely, achieving targets for three modifiable risk factors: LDL-C, non–HDL-C, and apo B. Such low achievement was found in a large proportion (one third) of very high-risk T2DM patients despite very low on-statin LDL-C levels.[93] Given currently available medications, combined attainment of LDL-C, non–HDL-C, and apo B targets will require titration or permutation of statins, reinforcement of therapeutic lifestyle changes, and/or combination lipid-lowering therapy.

Thus, a lipid-lowering therapy policy solely guided by an LDL-C target may not systematically deliver synchronous attainment of all atherogenic cholesterol targets, because lipid-lowering drugs do not produce strictly proportional decreases in LDL-C, LDL-P, non–HDL-C, and apo B.[93,156–158] More than 90% of circulating apo B belongs to LDL-Ps, which account for the bulk of non–HDL-C, meaning that discordant rates of achievement of targets for LDL-C versus apo B and/or non–HDL-C hints at potential unaddressed modifiable residual CV risk. Many recommendations include evaluation of and targeting therapy toward other non-LDL components of dyslipidemia, especially raised TGs and/or low HDL-C in subgroups with high CHD risk once LDL-C is at target. Along these lines, the lower the on-treatment LDL-C level achieved, the more likely that all four critical variables used to assess hypercholesterolemia (LDL-C, LDL-P, non–HDL-C, and apo B) will attain their respective targets.

With regard to baseline and on-treatment non–HDL-C and apo B levels and LDL-C, a joint consensus statement issued by the ADA and the ACC Foundation recommends two sets of triple targets for patients at high or very high cardiometabolic risk, respectively. LDL-C, non–HDL-C, and apo B levels below 100 mg/dL (<2.6 mmol/L), below 130 mg/dL (<3.4 mmol/L), and below 90 mg/dL, respectively, are recommended for patients with DM but without major CHD risk factors. LDL-C, non–HDL-C, and apo B levels below 70 mg/dL (<1.8 mmol/L), below 100 mg/dL (<2.6 mmol/L), and below 80 mg/dL, respectively, are recommended for patients with the highest CHD risk—that is, known CHD or DM plus one or more additional major CHD risk factors.[105]

Regarding individual components of atherogenic dyslipidemia, or the presence of atherogenic dyslipidemia in high-risk patients reaching recommended levels of LDL-C, a recent EAS consensus statement recommends for male and female patients with TGs of 150 mg/dL (≥1.7 mmol/L) or higher and/or HDL-C below 40 mg/dL (<1.0 mmol/L) the consideration of intensified LDL-C lowering (the largest decrease being reached by maximizing statin therapy and/or the addition of ezetimibe) or combination of lipid-lowering therapy with niacin (although currently not marketed in Europe and the United States) or a fibrate—after intensifying therapeutic lifestyle changes, addressing secondary dyslipidemias, and checking patient compliance. Based on clinical outcome and safety data for combined statin plus fibrate therapies, fenofibrate is the preferred fibrate among the class to be added to a statin.[83–85,88,89,108,159]

Titration of the statin dose or use of more potent statins are options most often used when further reduction in LDL-particle concentration is contemplated. Other combination therapies can also be used in selected patients, associating a statin (in addition to therapeutic lifestyle changes) with ezetimibe, niacin, or fibrates to reach all LDL-related targets. In addition, such combinatory strategies can contribute to improvement in other non-LDL features of diabetic dyslipidemia. Determining whether this will reduce CHD outcomes will require dedicated outcome studies with DM patients for each association.

Unmet Clinical Needs and Future Directions

At present, results from trials evaluating the effects of lipid-lowering medications other than (or added to) statins on CHD outcomes have been either disappointing or inconclusive, especially when baseline LDL-C was normal or controlled with statins (with or without ezetimibe) and/or whenever the annual CV event rate during follow-up was

relatively low compared with older landmark trials. Regarding statins, evidence of the effectiveness of the entire class, in terms of reduction of occurrence of composite primary outcomes, is undeniable in DM patients.

The presently unmet need for definitive proof of efficacy of current lipid-lowering drugs on all components of lipid-related CHD in patients with DM is attributable to a variety of causes. There have been few DM-specific trials; most of the available evidence has been derived from post hoc analyses of DM subgroups. Within the aggregate DM dataset, the relatively few cumulative events available for analyses challenge statistical power for efficacy assessments, especially for assessment of effects on individual components of the endpoints analyzed (**Table 15-7**). This is confounded by the inclusion in several trials of patients at lower risk than planned, resulting in low event rates and marginal statistical

TABLE 15-7 Statin Efficacy on Coronary Heart Disease Outcomes in Patients with Diabetes Mellitus (DM)*

DRUG(s)	DOSE (mg)	ACRONYM	OUTCOME	HR	*P*	5-YEAR NNT
Simvastatin	20-40	4S (DM subgroup)	All MI	0.27		
Atorvastatin	23.7	GREACE (DM subgroup)	Fatal CHD	0.38	= 0.042	15
Atorvastatin	10	CARDS	Fatal MI	0.39		
Atorvastatin	23.7	GREACE (DM subgroup)	Primary	0.41	< 0.0001	3
Atorvastatin	80	PROVE IT–TIMI 22 (DM subgroup)	UAP	0.42	= 0.003	9
Atorvastatin	23.7	GREACE (DM subgroup)	All CV events	0.43	= 0.0001	4
Atorvastatin	23.7	GREACE (DM subgroup)	All-cause mortality	0.48	= 0.049	14
Atorvastatin	80	SPARCL (DM subgroup)	Total CHD	0.49	= 0.01	23
Pravastatin	40	CARE (DM subgroup)	Fatal MI	0.54		
Simvastatin	20-40	4S (DM subgroup)	All-cause mortality	0.58		
Simvastatin	20-40	4S (DM subgroup)	Primary	0.58	= 0.087	
Atorvastatin	10	CARDS	Nonfatal MI	0.60		
Simvastatin	40	HPS—MRC/BHF (DM subgroup)	Nonfatal MI	0.64	= 0.0002	49
Atorvastatin	10	CARDS	Primary	0.65	= 0.001	24
Simvastatin	20-40	4S (DM subgroup)	Fatal CHD	0.65	= 0.242	
Simvastatin	20-40	4S (DM subgroup)	Total CHD	0.65	= 0.015	5
Atorvastatin	10	CARDS	ACS	0.65		
Atorvastatin	80	SPARCL (DM subgroup)	All CV events	0.67	= 0.01	11
Simvastatin	20-40	4S (DM subgroup)	PCI, CABG	0.69	= 0.265	
Atorvastatin	10	CARDS	PCI, CABG	0.70		
Pravastatin	40	CARE (DM subgroup)	PCI, CABG	0.71	= 0.04	9
Atorvastatin	10	CARDS	All CV events	0.71	= 0.001	20
Atorvastatin	20	4D	Fatal MI	0.72		
Rosuvastatin	10	AURORA (DM subgroup)	Primary	0.72	= 0.008	7
Atorvastatin	10	CARDS	All-cause mortality	0.73	= 0.059	
Atorvastatin	10	ASPEN	All MI	0.74	= 0.1	
Rosuvastatin	10	AURORA (DM subgroup)	Fatal CHD	0.74		
Atorvastatin	80	TNT (DM subgroup)	Fatal CHD	0.74	= 0.203	
Simvastatin	40	HPS—MRC/BHF (DM subgroup)	Total CHD	0.74	< 0.0001	29
Atorvastatin	80	PROVE IT–TIMI 22 (DM subgroup)	All MI	0.75	= 0.11	
Atorvastatin	80	TNT (DM subgroup)	Primary	0.76	= 0.026	22
Atorvastatin	10	CARDS	UAP	0.77		
Atorvastatin	10	ASCOT-LLA (DM subgroup)	All CV events	0.77	= 0.036	24
Pravastatin	40	CARE (DM subgroup)	All MI	0.77		
Pravastatin	40	CARE (DM subgroup)	Total CHD	0.77	= .05	
Atorvastatin	10	ASCOT-LLA (DM subgroup)	Primary	0.78	= .036	25
Pravastatin	40	CARE (DM subgroup)	Primary	0.78	< .0001	12
Atorvastatin	80	TNT (DM subgroup)	Nonfatal MI	0.79	= .202	
Atorvastatin	80	TNT (DM subgroup)	All CV death	0.79	> .05	
Atorvastatin	20	4D	PCI, CABG	0.79		
Simvastatin	40	HPS—MRC/BHF (DM subgroup)	Primary	0.81	< .0001	20
Atorvastatin	80	TNT (DM subgroup)	Total CHD	0.81		
Simvastatin	40	HPS—MRC/BHF (DM subgroup)	Fatal CHD	0.81	= .02	63

TABLE 15-7 Statin Efficacy on Coronary Heart Disease Outcomes in Patients with Diabetes Mellitus (DM)—cont'd

DRUG(s)	DOSE (mg)	ACRONYM	OUTCOME	HR	P	5-YEAR NNT
Atorvastatin	10	ASPEN	Sudden death	0.81		
Pravastatin	40	CARE (DM subgroup)	Nonfatal MI	0.82		
Atorvastatin	20	4D	Fatal CHD	0.83	= .08	
Atorvastatin	80	TNT (DM subgroup)	All CV events	0.85	= .044	22
Atorvastatin	80	PROVE IT–TIMI 22 (DM subgroup)	Primary	0.88	= .28	
Pravastatin	40	CARE (DM subgroup)	UAP	0.89		
Atorvastatin	20	4D	Nonfatal MI	0.91	= .42	
Atorvastatin	10	ASPEN	Primary	0.9	= .341	
Atorvastatin	20	4D	Sudden death	0.95		
Atorvastatin	20	4D	All-cause mortality	0.95	= .33	
Atorvastatin	80	PROVE IT–TIMI 22 (DM subgroup)	All-cause mortality	0.95	= .75	
Atorvastatin	20	4D	Primary	0.96	= .37	
Atorvastatin	10	ASPEN	PCI, CABG	0.97		
Pravastatin	40	CARE (DM subgroup)	Fatal CHD	0.97		
Atorvastatin	10	ASPEN	All CV death	1.02		NA
Atorvastatin	10	ASPEN	UAP	1.02		NA
Atorvastatin	80	SPARCL (DM subgroup)	All-cause mortality	1.03	= .82	NA
Atorvastatin	80	TNT (DM subgroup)	All-cause mortality	1.09		NA
Atorvastatin	10	CARDS	Sudden death	2.47		NA

See **Table 15-1** for acronym definition and references.
NA = not applicable (HR >1.00); UAP = unstable angina pectoris.
*Trials listed by descending order of HR reduction;

power, and use of suboptimal eligibility criteria in the context of the study medication being evaluated. For example, the inclusion of patients in the FIELD or ACCORD-Lipid trials without requiring hypertriglyceridemia and/or atherogenic dyslipidemia remains difficult to defend, given the prevalence of atherogenic dyslipidemia in DM patients and the mechanism of action of the PPAR-α agonist tested.

SUMMARY

Patients with DM, especially T2DM, are at very high risk of CHD, particularly because of the high prevalence of LDL-C and non–LDL-C dyslipidemias and other comorbidities. Large clinical trials have unambiguously demonstrated the elevated risk for CHD in DM, and the significant CHD risk reduction that can be achieved by statins in both primary and secondary prevention populations. With regard to other lipid-lowering medications, instead of or added to statin therapy, there are currently insufficient data to guide clinical recommendations and use, overall and in DM populations specifically. Therefore, support for pharmacologic treatment of diabetic dyslipidemia remains grounded on pathophysiological considerations, epidemiologic associations, and signals based on post hoc analyses from selected clinical trials. All guidelines recognize a higher risk of CHD in patients with DM, even in situations of primary prevention, compared with nondiabetic patients. This recognition underlies the current recommendations, generally converging, which advocate targeting of LDL-C as the major modifiable lipid risk factor for CHD in DM patients, although there is ongoing debate regarding the clinical relevance of the concept of therapeutic target values for LDL-C versus matching intensity of drug with estimated CVD risk. In addition, there remains debate about whether other therapeutic targets should be pursued, such as non–HDL-C, apo B, TGs, and HDL-C in patients treated with lipid-lowering agents.[160]

The lipid-lowering effects of drugs under development make them potentially attractive to improve both standard care and other aspects of dyslipidemia management in patients with DM. This includes screening for and targeting the high residual vascular risk that persists in DM patients whose LDL-C is controlled on statins and that is present in patients with inadequate LDL-C levels and the risk of persistently high LDL-C in patients with severe statin intolerance. The future challenge will be to identify and to bring a greater majority of patients with DM to meet their personalized optimal levels of LDL-C and non–LDL-C, to further reduce the occurrence of CHD.

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16 Effect of Antiplatelet Therapy on Coronary Heart Disease Risk in Patients with Diabetes Mellitus



Michelle L. O'Donoghue and Deepak L. Bhatt

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Platelets play a central role in the pathobiology of atherogenesis and atherothrombosis. Therefore therapies that are directed toward platelet inhibition are widely used in patients with established coronary heart disease (CHD) or in moderate- to high-risk individuals for primary prevention of cardiovascular (CV) events.[1] As our armamentarium of potent antiplatelet therapies continues to expand, there is growing interest in identifying the appropriate groups of patients who will derive the greatest benefit from more potent therapies. To that end, several studies over the past few decades have highlighted that individuals with diabetes mellitus (DM) exhibit abnormalities in platelet function that place them at increased risk of adverse outcomes, as compared with their nondiabetic counterparts (see also **Chapter 10**).[2] Although the mechanisms that contribute to platelet hyperreactivity in diabetic patients continue to be elucidated, it appears that diabetic platelets are characterized by the dysregulation of several signaling pathways that occur both at the level of the platelet receptor and with subsequent downstream signaling.[3,4] In addition, glycosylation may impair endothelial function and promote oxidative stress, thereby further promoting platelet reactivity and procoagulant activity.[1] There is therefore a priori biologic plausibility to support the concept that diabetic patients may derive enhanced benefit from particular therapies directed toward blocking the platelet. However, differences in platelet biology in diabetic patients may also contribute to diminished antiplatelet drug responsiveness. This chapter reviews the use of established and novel oral antiplatelet therapies in diabetic patients for use in primary or secondary prevention of CV events.

ASPIRIN

To date, aspirin remains the cornerstone of antiplatelet therapy in the primary and secondary prevention of CV events. Aspirin selectively acetylates the hydroxyl group of a serine residue leading to irreversible inhibition of the cyclooxygenase-1 (COX-1) enzyme.[5] In turn, inhibition of the COX-1 enzyme blocks downstream production of thromboxane A_2 (TXA_2; **Fig. 16-1**), thereby preventing thromboxane-mediated platelet aggregation and vasoconstriction. Because the platelet is enucleate, it is unable to resynthesize COX-1 and the effects of aspirin persist throughout the lifetime of the platelet.[5]

Aspirin in Primary Prevention

Although its role in secondary prevention is well established, the clinical efficacy of aspirin in primary prevention remains an ongoing area of investigation. Several large primary prevention trials of aspirin have been conducted in the general population, and investigators have subsequently evaluated the benefit of aspirin within their diabetic subgroups.[6–8] Although limited by small numbers of diabetic patients and by post hoc design, many trials were able to demonstrate a consistent benefit of aspirin in the primary prevention of CV events for both their diabetic and nondiabetic patients.[6,7] These results were supported by the Early Treatment Diabetic Retinopathy Study (ETDRS), which included a mixed population of 3711 patients with DM with or without a history of CHD who were randomized to aspirin 650 mg daily or placebo.[9] Although aspirin did not reduce the primary endpoint of all-cause death (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.75-1.11), a favorable trend was observed toward a reduction in fatal or nonfatal myocardial infarction (MI) at 5 years that did not achieve statistical significance (HR 0.83, 95% CI 0.66-1.04).[9]

In contrast, a benefit for aspirin could not be definitively demonstrated in diabetic patients enrolled in the Primary Prevention Project (PPP), a randomized trial of low-dose aspirin (100 mg daily) versus placebo in 4495 patients with one or more CV risk factors.[8] Although underpowered to detect a significant benefit within the diabetic subgroup (n = 1031), the investigators were unable to demonstrate a significant reduction in CV death, MI, or stroke in diabetic patients (HR 0.90, 95% CI 0.50-1.62) or in total CV events (HR 0.89, 95% CI 0.62-1.26). Moreover, an unfavorable trend was observed toward an increased risk of CV death (HR 1.23, 95% CI 0.69-2.19) in aspirin-treated diabetic patients. In contrast, a more consistent benefit was seen with aspirin in nondiabetic patients with regard to reduction in the risk of CV death, MI, or stroke (HR 0.59, 95% CI 0.37-0.94), total CV events (HR 0.69, 95% CI 0.53-0.90), and CV death (HR 0.32, 95% CI 0.14-0.72).[8]

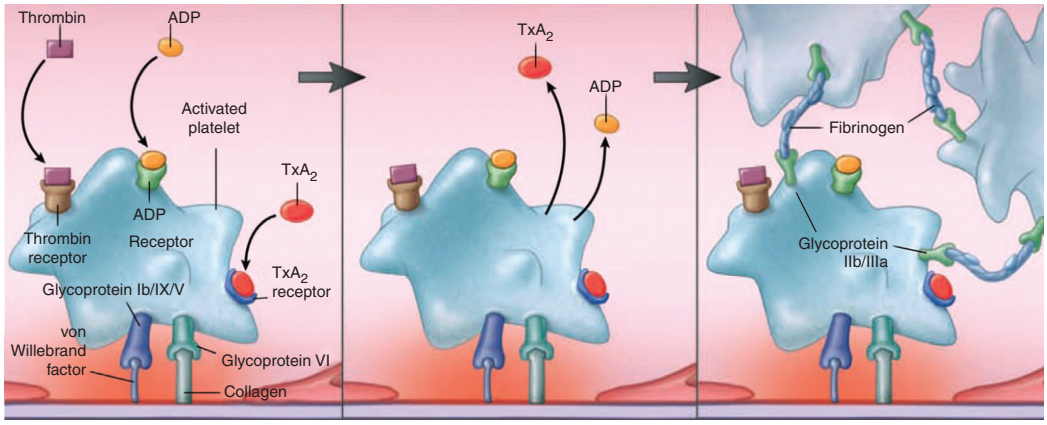


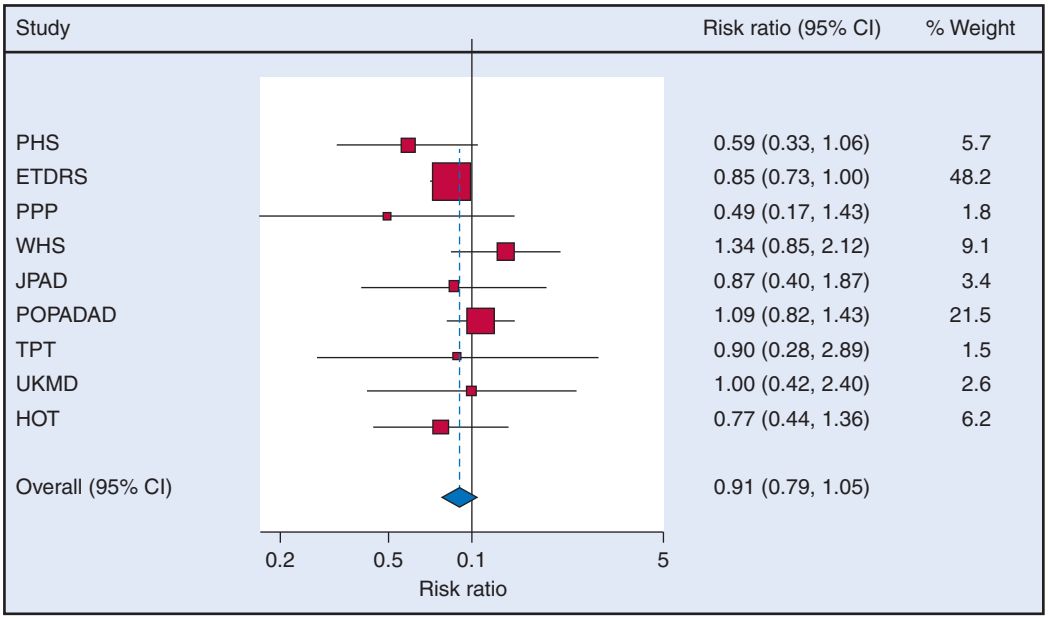
FIGURE 16-1 The platelet has multiple ligands that contribute to pathways leading to platelet activation including thrombin, adenosine diphosphate (ADP), von Willebrand factor, and thromboxane A_2 (TXA_2). The activated platelet then releases prothrombotic factors including ADP and TXA_2, thereby further amplifying platelet activation. A platelet latticework is formed when fibrinogen cross-links activated platelets via the glycoprotein IIb/IIIa receptor. The P2Y12 subtype of the ADP receptor is the site of action for established and novel compounds, including ticlopidine, clopidogrel, prasugrel, ticagrelor, and elinogrel. *(Modified from Bhatt DL: Intensifying platelet inhibition—navigating between Scylla and Charybdis,* N Engl J Med *357:2078-2081, 2007.)*

Because individual trials of aspirin therapy in primary prevention enrolled relatively few diabetic patients, De Berardis and colleagues combined data from six trials and 10,117 patients to examine the clinical efficacy of aspirin to reduce major CV events in primary prevention.[10] The meta-analysis demonstrated a benefit of aspirin in the overall study population, yet the authors were unable to identify a statistically significant benefit in the diabetic subgroup. Although a directional trend was observed, aspirin did not significantly reduce the risk of major CV events in diabetic patients as compared with placebo (HR 0.90, 95% CI 0.81-1.00). Furthermore, aspirin did not reduce either CV mortality (HR 0.94, 95% CI 0.72-1.23) or all-cause mortality (HR 0.93, 95% CI 0.82-1.05) in diabetic patients. However, limitations of the meta-analysis included evidence of significant heterogeneity across trials for key endpoints including MI. To that end, aspirin significantly reduced the risk of MI in men (HR 0.57, 95% CI 0.34-0.94), but did not reduce the risk of MI in women (HR 1.08, 95% CI 0.71-1.65; *P* for interaction = 0.056). Because women had a higher prevalence of DM, sex-restricted enrollment in some of the trials may have contributed to the observed heterogeneity.[6,11] Consistent findings were observed in an updated meta-analysis that included individuals with DM across nine trials of aspirin in primary prevention. Aspirin reduced the risk of CHD events by 9%, but the results were not statistically significant (relative risk 0.91, 95% CI 0.79 -1.05). Similarly, the use of aspirin was associated with a nonsignificant 10% reduction in the risk of stroke (relative risk 0.90, 95% CI 0.71-1.13; **Fig. 16-2**).[12] These findings therefore raised concerns that the antiplatelet effects of aspirin were insufficient to attenuate risk of CV events in diabetic patients with baseline abnormalities in platelet function.

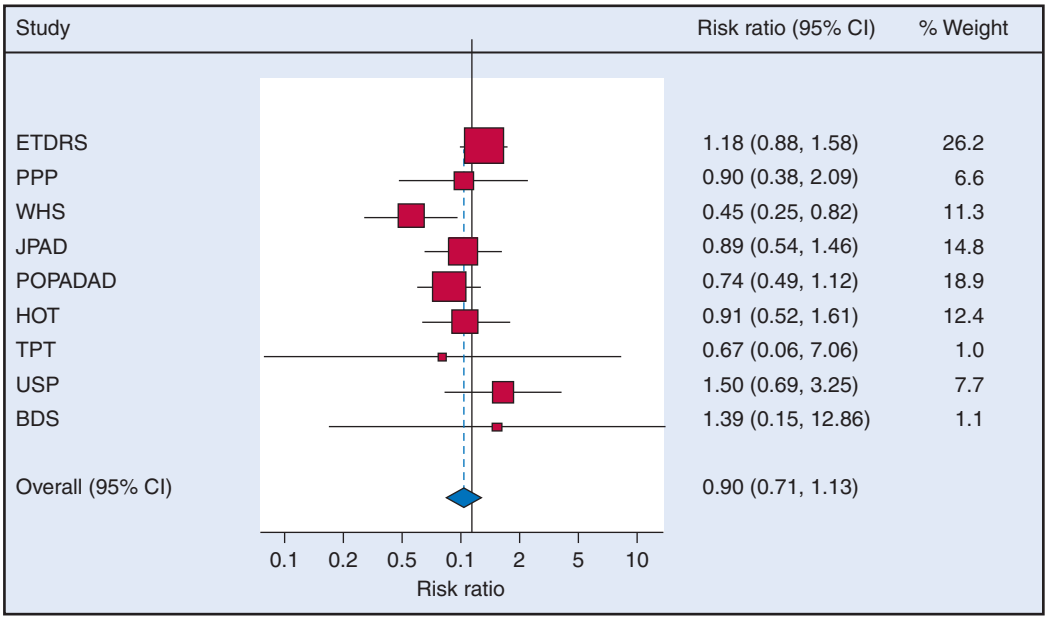
Because subgroup analyses from randomized trials may yield spurious results, dedicated trials of aspirin for primary prevention in diabetic patients have since been completed or are still ongoing. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study was the first prospectively designed trial to evaluate the use of low-dose aspirin (81 or 100 mg daily) versus placebo in 2539 type 2 diabetic patients in Japan aged 30 to 85 years and without a known history of atherosclerotic disease.[13] After a median of 4.37 years, only 154 atherosclerotic events (including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease [PAD]) occurred during follow-up and the trial was therefore unable to demonstrate clinical efficacy with aspirin in diabetic patients despite a directional trend (HR 0.80, 95% CI 0.58-1.10, $P = 0.16$).[13] In addition to being underpowered, other limitations of the trial included its open label design, which introduced the possibility of bias. However, among the subgroup of patients older than 65 years, aspirin reduced the risk of atherosclerotic events by 32% ($P = 0.047$). The incidence of hemorrhagic stroke or gastrointestinal (GI) bleeding was low and did not differ significantly between groups.[13]

Subsequently, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial evaluated the efficacy of low-dose aspirin (100 mg daily) versus placebo in 1276 adults in Scotland older than 40 years with type 1 or type 2 DM and an ankle brachial pressure index below 0.99 in the absence of symptomatic CV disease.[14] Although the trial was relatively small, the incidence of CV events (death from congestive heart failure [CHF] or stroke, nonfatal MI or stroke, or amputation because of critical limb ischemia) was almost identical between treatment arms during a median of 6.7 years follow-up (116 versus 117 events; HR 0.98, 95% CI 0.76-1.26). Aspirin did not reduce the risk of death from CHD or stroke (HR 1.23, 95% CI 0.79-1.93). GI bleeding was infrequent, and its incidence did not differ between groups.[14]

In light of these conflicting data, the use of aspirin in primary prevention continues to be a topic of debate. In particular, any signal suggesting efficacy must be weighed against the potential risks of treatment. In a large population-based cohort of individuals in Italy, the use of aspirin was associated with a relative 55% increased incidence of major bleeding over a median of 5.7 years in the overall cohort, as compared with patients not taking aspirin.[15] The risk of bleeding was increased in individuals over the age of 70, those with a higher risk of GI disease, and by concomitant use of NSAIDs. Irrespective of aspirin use, patients with DM were observed to have a 36% higher incidence of major bleeding episodes, including an increased risk of GI and intracranial bleeding, as compared with nondiabetic patients.[15] Of interest, the use of aspirin did not appear to



A



B

FIGURE 16-2 A meta-analysis of randomized trials that examined the effects of aspirin on the risk on CHD events **(A)** and stroke **(B)** in diabetic patients without an overt history of CV disease. Although there was a directional trend toward a reduction in the risk of CHD events and stroke with aspirin in diabetic patients, this benefit was not statistically significant. *(From Pignone M, Alberts MJ, Colwell JA, et al: Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation,* Circulation *121:2694-2701, 2010.)*

be associated with an increased risk of bleeding for diabetic patients. However, it remains unknown whether the absence of a bleeding signal with aspirin in diabetic patients might be explained by a diminished pharmacodynamic response to aspirin in diabetic patients with abnormal platelet biology, or attributable to other factors.

Based on the weight of the evidence to date, the American Diabetes Association (ADA) updated its recommendations in 2010 to consider low-dose aspirin therapy (75 to 162 mg/day) in primary prevention in diabetic individuals (men older than 50 years, women older than 60 years) at increased CV risk (10-year risk greater than 10%) with at least one or more major CV risk factor including family history of CV disease, hypertension, albuminuria, dyslipidemia, or current tobacco use (**Table 16-1**).[16] In 2010, an expert panel that included representatives from the ADA, the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA) issued similar recommendations that included the use of aspirin (75 to 162 mg/day) in individuals (men older than 50 years, women older than 60 years) at increased CV risk (10-year risk >10%) and with established CV risk factors, who were not believed to be at increased risk of bleeding.[12] They also noted that low-dose (75-162 mg/day) aspirin could be considered for those with

TABLE 16-1 Summary of Recommendations Regarding the Use of Aspirin in Primary Prevention in Diabetic Individuals

ORGANIZATION	YEAR	RECOMMENDATION
American Diabetes Association[16]	2014	Consider aspirin therapy (75-162 mg/day) as a primary prevention strategy in those with type 1 or type 2 DM at increased CV risk (10-year risk >10%). This includes most men older than 50 years or women older than 60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (Level of evidence: C) There is not sufficient evidence to recommend aspirin for primary prevention in lower-risk individuals, such as men younger than 50 years or women younger than 60 years without other major risk factors. In patients in these age groups with multiple other risk factors, clinical judgment is required. (C)
ADA, American Heart Association (AHA), American College of Cardiology Foundation (ACCF)[12]	2010	Low-dose (75-162 mg/day) aspirin use for prevention is reasonable for adults with DM and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events >10%) and who are not at increased risk for bleeding (based on a history of previous GI bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as NSAIDS or warfarin). Adults with diabetes who are at increased CVD risk include most men over age 50 years and women over age 60 years who have one or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria. (ACCF/AHA Class IIa, level of evidence B; ADA level of evidence C) Aspirin should not be recommended for CVD prevention for adults with DM at low CVD risk (men younger than 50 years and women younger than 60 years with no major additional CVD risk factors; 10-year CVD risk under 5%) because the potential adverse effects from bleeding offset the potential benefits. (ACCF/AHA Class III, level of evidence C; ADA level of evidence C) Low-dose (75-162 mg/day) aspirin use for prevention might be considered for those with DM at intermediate CVD risk (younger patients with one or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5%-10%) until further research is available. (ACCF/AHA Class IIb, level of evidence C; ADA level of evidence E)
U.S. Preventive Services Task Force[17,18]	2009	In men aged 45-79 years, encourage aspirin use when potential CVD benefit (MIs prevented) outweighs the potential harm of GI hemorrhage (irrespective of whether the individual has DM). In women aged 55-79 years, encourage aspirin use when potential CVD benefit (ischemic strokes prevented) outweighs the potential harm of gastrointestinal hemorrhage (irrespective of whether the individual has DM). Do not encourage aspirin use for MI prevention in men younger than 45 years or for stroke prevention in women younger than 55 years (irrespective of whether the individual has DM). There is insufficient evidence to recommend the use of aspirin for primary prevention in individuals aged 80 years or older.
European Society of Cardiology[19]	2012	Antiplatelet therapy with aspirin is not recommended for people with DM who do not have clinical evidence of atherosclerotic disease. (Level of evidence A)

CVD = Cardiovascular disease; NSAIDs = nonsteroidal anti-inflammatory drugs.

DM at intermediate CVD risk (younger patients with one or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5% to 10%).[12] Aspirin is not recommended in diabetic patients younger than 21 years because of the risk of Reye syndrome, and the role of aspirin in diabetic patients younger than 30 years remains largely untested. The U.S. Preventive Services Task Force has recommended aspirin use in men aged 45 to 79 years and women 55 to 79 years but has not differentiated their recommendations on the presence or absence of DM.[17,18] In contrast, the European Society of Cardiology guidelines for CV prevention do not recommend aspirin for primary prevention regardless of baseline risk, including in patients with DM (see **Table 16-1**).[19]

Because trials to date have yielded inconclusive results, the net clinical benefit of aspirin in the primary prevention of CV events in diabetic patients remains an ongoing area of investigation (**Table 16-2**). The Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D, ISRCTN48110081) study is an open-label trial that is randomizing individuals with type 1 or type 2 DM and without clinical evidence of vascular disease to aspirin with statin or statin alone to evaluate whether aspirin will reduce a first CV event. Similarly, the ongoing ASCEND (A Study of Cardiovascular Events in Diabetes) trial (clinicaltrials.gov NCT00135226) is randomizing patients with DM and without known occlusive arterial disease to 100 mg of aspirin daily versus placebo and/or supplementation with 1 g of omega-3 fatty acids daily or placebo.

Aspirin in Secondary Prevention

Although the role of aspirin in primary prevention continues to be investigated, the use of aspirin in stable and unstable secondary prevention is well established. Whereas smaller studies had been suggestive, the first randomized trial that definitively demonstrated aspirin's efficacy in patients with acute MI was the Second International Study of Infarct Survival (ISIS-2), which demonstrated a 23% reduction in the odds of vascular death with aspirin at 5 weeks when compared with placebo.[20] Subsequent trials have since demonstrated a consistent benefit for aspirin across the spectrum of acute coronary syndrome (ACS) (see also **Chapter 21**).[1]

The Antithrombotic Trialists' Collaboration (ATC) combined data from 287 secondary prevention studies of oral antiplatelet agents, mostly aspirin, and included a total of 212,000 individuals with acute vascular disease, established vascular disease, or risk factors for vascular disease.[21]

TABLE 16-2 Ongoing Trials of Aspirin for Primary Prevention in Individuals with Type 1 or Type 2 DM

TRIAL NAME	DESIGN	POPULATION	INTERVENTION	OUTCOME
Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; ISRCTN48110081)	Open label, randomized, parallel group	Approximately 5170 patients; type 1 or type 2 DM without clinical evidence of vascular disease and with an indication for statin therapy	Aspirin (100 mg/day) plus simvastatin versus simvastatin alone	CV death, MI, stroke, or CV hospitalization
A Study of Cardiovascular Events in Diabetes trial (ASCEND; clinicaltrials.gov NCT00135226)	Double-blind, 2 × 2 factorial randomized design	Approximately 15,480 patients; type 1 or type 2 DM, older than 40 years, and without known history of vascular disease	Aspirin (100 mg/day) versus placebo (2 × 2: 1 g/day omega-3 ethyl esters versus placebo)	Vascular death, MI, or stroke (excluding cerebral hemorrhage)

Overall, in patients with established CV disease, antiplatelet therapy reduced the odds of recurrent CV events by 22% and of nonfatal stroke by 25%. Although individuals with DM had a higher absolute event rate than nondiabetic patients, the relative benefit of antiplatelet therapy toward reducing vascular events was consistent across patient groups. For every 1000 diabetic patients treated with aspirin, it was estimated that 42 vascular events could be prevented with use of antiplatelet therapy.[21]

Of note, it was observed in the ATC analysis that lower doses of aspirin (75 to 150 mg/day) appeared to be as efficacious as high doses of aspirin (>150 mg/day). Furthermore, the use of lower doses of aspirin was associated with a reduced risk of bleeding complications as compared with higher doses. The evidence to support the use of lower doses of aspirin was also supported by an observational analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial that demonstrated that aspirin doses exceeding 100 mg daily were not associated with increased efficacy as compared with lower doses in patients with stable CV disease or CV risk factors.[22] Moreover, there was an unfavorable trend toward a higher risk of CV death, MI, or stroke (adjusted HR 1.16, 95% CI 0.93-1.14) and increased risk of severe or life-threatening bleeding (adjusted HR 1.30, 95% CI 0.83-2.04) when aspirin doses above 100 mg daily were combined with clopidogrel. More recently, the question of optimal aspirin dosage was directly addressed in a randomized clinical trial of low-dose (325 mg loading dose, 75 to 100 mg daily) versus higher-dose aspirin (325 mg loading dose, 300 to 325 mg daily) in patients with ACS.[23] The use of higher-dose aspirin did not reduce the risk of CV death, MI, or stroke (HR 0.97, 95% CI 0.86-1.09) as compared with low-dose aspirin after 30 days, but increased the risk of minor bleeding by 13% (HR 1.13, 95% CI 1.00-1.27, $P = 0.04$).[23]

The ADA currently recommends the use of low-dose aspirin (75 to 162 mg/day) for secondary prevention of CV events (including stroke) in all diabetic patients without contraindication. Based on the strength of the data, the use of low-dose aspirin is now supported by the ACC/AHA guidelines in patients after non–ST-elevation ACS or percutaneous coronary intervention (PCI) (see also **Chapter 21**).[24,25]

P2Y12 RECEPTOR ANTAGONISTS

Although CV events are not always platelet mediated, platelet activation and aggregation may occur in the presence of aspirin through pathways unrelated to TXA_2 (see **Fig. 16-1**). Therefore this unmet need has prompted the development of alternate oral antiplatelet drugs to use in combination with or as a substitute for aspirin. The P2Y1 and P2Y12 receptors on the platelet cell surface play a tandem role in contributing to platelet activation and aggregation via adenosine diphosphate (ADP)–dependent pathways. The P2Y1 receptor is responsible for an initial weak and transient phase of platelet aggregation, whereas ADP signaling pathways mediated by G_i-coupled P2Y12 receptor activation lead to sustained platelet aggregation and stabilization of the platelet aggregate.[26] The P2Y12 receptor is the target for many established and novel antiplatelet agents, including ticlopidine, clopidogrel, prasugrel, ticagrelor, elinogrel, and cangrelor.

Ticlopidine

Ticlopidine was the first thienopyridine to be approved for clinical use, in 1991. It is a first-generation thienopyridine that irreversibly blocks the ADP P2Y12 receptor and thereby prevents platelet activation and aggregation mediated by ADP signaling pathways.[27] When combined with aspirin, ticlopidine has been shown to reduce the risk of CV events in patients undergoing coronary stenting as compared with aspirin monotherapy or aspirin with warfarin.[27] However, an unfavorable safety profile (including risk of neutropenia) and slow onset of action led the way for clopidogrel to emerge shortly thereafter as the preferred thienopyridine in appropriate settings.

Clopidogrel

When compared with ticlopidine, clopidogrel has been shown to have similar efficacy in addition to improved safety and tolerability[27] and faster pharmacodynamic effects after a loading dose.[28] In a meta-analysis that combined data from 13,995 patients in randomized trials and registries of ticlopidine versus clopidogrel, the use of clopidogrel was associated with a significant reduction in mortality and recurrent ischemic events when compared with ticlopidine and had fewer side effects.[29] The efficacy of clopidogrel monotherapy (75 mg/day) versus aspirin (325 mg/day) in secondary prevention was evaluated in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.[30] The CAPRIE trial compared clopidogrel (75 mg/day) versus aspirin (325 mg/day) in 19,185 patients with established atherosclerotic disease, including recent MI, recent stroke, or symptomatic PAD. Overall, clopidogrel monotherapy significantly reduced the risk of vascular death, MI, or ischemic stroke by 8.7% compared with aspirin alone ($P = 0.043$) and reduced the risk of GI bleeding ($P = 0.05$).[30] Patients with DM in the trial (n = 3866) were observed to have approximately a threefold higher event rate compared with their nondiabetic counterparts.[31] Overall, the relative risk reduction (RRR) of clopidogrel versus aspirin for reducing

vascular events was statistically similar in diabetic and nondiabetic patients (12.5% versus 6.1%, respectively, *P* for interaction = 0.36).[31] However, because of the higher absolute event rate in diabetic patients and the trend toward a greater RRR, clopidogrel conferred a greater absolute benefit in diabetic patients. To that end, the number of events (vascular death, MI, stroke, rehospitalization with ischemia, bleeding) prevented per 1000 patients per year was 21 in diabetic patients versus 9 in nondiabetic patients treated with clopidogrel as compared with aspirin. The absolute benefit of clopidogrel further improved to 38 events prevented per 1000 patients per year in insulin-treated patients with diabetes treated with clopidogrel as compared with aspirin (**Fig. 16-3**).[31] Following the publication of the CAPRIE findings, the ADA issued recommendations that clopidogrel be used as monotherapy in very high-risk diabetic patients and as an alternative to aspirin in intolerant patients.[32]

Although individuals with DM have higher platelet reactivity, randomized trials have been unable to demonstrate a greater relative benefit for clopidogrel in diabetic versus nondiabetic patients. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial enrolled 12,562 patients with non–ST-elevation ACS and randomized them to clopidogrel versus placebo on a background of aspirin for up to 1 year.[33] After a mean of 9 months, clopidogrel reduced the risk of vascular death, MI, or stroke by 20% compared with placebo (HR 0.80, 95% CI 0.72-0.90). This clinical benefit was associated with a 38% increase in the risk of major bleeding (3.7% versus 2.7%, $P < 0.001$) but no increase in the risk of fatal bleeding.[33] The benefit of clopidogrel appeared early but was maintained beyond 30 days (HR 0.82; 95% CI 0.70-0.95). Consistent with prior studies, diabetic patients in the trial (n = 2840) were observed to have almost a two-fold higher rate of CV events (14.2% versus 7.9%) as compared with their nondiabetic counterparts, thereby translating into a greater absolute benefit from clopidogrel. However, the relative benefit of clopidogrel was grossly similar in diabetic and nondiabetic patients with an approximate 17% RRR in the primary endpoint in diabetic patients, as compared with 20% in the overall population.[33]

More recently, the clinical efficacy of clopidogrel was evaluated in a nonrandomized analysis of a large nationwide Danish registry of patients who had survived 30 days after an MI.[34] After multivariable adjustment and propensity-score matching, clopidogrel was associated with a smaller reduction in all-cause mortality (adjusted HR 0.89, 95% CI 0.79-1.00 versus 0.75, 95% CI 0.70-0.80, *P* interaction = 0.001) and CV mortality (adjusted HR 0.93, 0.81-1.06 versus 0.77, 95% CI 0.72-0.83, *P* interaction = 0.01) in patients with DM, as compared with those who did not have diabetes. Clopidogrel was associated with only a marginal difference in the risk of death or reinfarction in either patient group (0.91, 0.87-0.96 versus 1.00, 0.91-1.10, *P* interaction = 0.08).[34] However, this differential association for clopidogrel between diabetic and nondiabetic patients was not observed in patients undergoing PCI, and no differential association was observed between patient groups with regard to the efficacy of aspirin.[35] Limitations of this analysis included the fact that use of clopidogrel was not randomized and therefore there is the risk of confounding despite adjustments having been made for known confounders. Supporting this hypothesis, clopidogrel appeared to have a greater magnitude of association toward reduced risk of death as compared with the risk of reinfarction, a finding not supported by existing trials.[35]

Notwithstanding the limitations of a nonrandomized analysis, there are mechanistic data to support the hypothesis that clopidogrel may have diminished efficacy in diabetic patients. Pharmacodynamic studies have demonstrated that almost two thirds of diabetic patients have an inadequate response to clopidogrel.[36] Moreover, platelet aggregation on dual antiplatelet therapy is even further heightened in insulin-treated diabetic patients, as compared with those who do not require insulin therapy (**Fig. 16-4**).[37] The latter finding is perhaps explained by the fact that insulin inhibits platelet aggregation by suppressing the P2Y12 pathway. Because diabetic patients have a loss of responsiveness to insulin, there is subsequent upregulation of the P2Y12 pathway, leading to heightened platelet reactivity and diminished response to antiplatelet agents.

Multiple trials have examined the benefit of clopidogrel and the optimal timing of loading dose administration in patients undergoing PCI. Because clopidogrel is a prodrug, approximately 6 hours are required to attain steady state

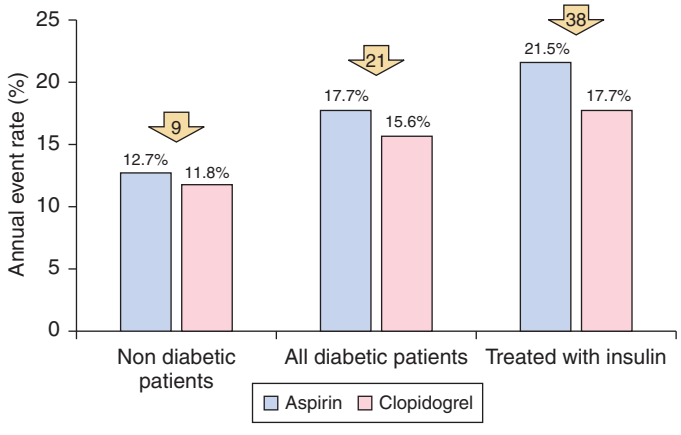


FIGURE 16-3 The number of events (vascular death, MI, stroke, or rehospitalization for ischemia or bleeding) prevented per 1000 patients per year treated with clopidogrel instead of aspirin in nondiabetic patients, all diabetic patients, and diabetic patients treated with insulin in the CAPRIE trial. *(Modified from Bhatt DL, Marso SP, Hirsch AT, et al: Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus,* Am J Cardiol *90:625-628, 2002.)*

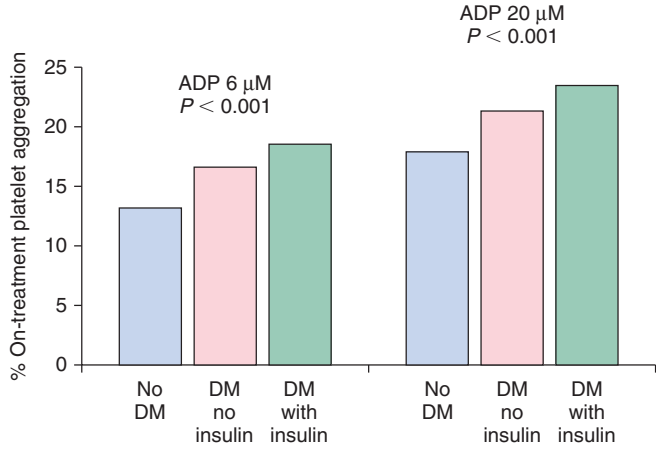


FIGURE 16-4 Platelet aggregation after stimulation with 6 μM and 20 μM adenosine diphosphate (ADP) in nondiabetic patients, non–insulin-treated diabetic patients, and insulin-dependent diabetic patients. on stable doses of dual antiplatelet therapy. *(Modified from Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment,* J Am Coll Cardiol *48:298-304, 2006.)*

concentrations after a 300-mg loading dose. The PCI-CURE substudy examined outcomes for those patients enrolled in the CURE trial who underwent PCI (see also **Chapter 21**).[38] The CURE trial enrolled 12,562 patients with non–ST-elevation acute coronary syndromes (NSTE-ACS) and randomized them to clopidogrel (300-mg loading dose, 75 mg daily) versus placebo on a background of aspirin. Those patients who were pretreated with clopidogrel before PCI and who continued clopidogrel for up to 1 year had a 31% lower risk of CV death or MI compared with patients who were not pretreated and who were treated for only 4 weeks after PCI. Although numerically smaller in magnitude, this benefit was comparable in diabetic patients in whom clopidogrel reduced the risk of CV death or MI by 23% compared with placebo after PCI.[38]

Similar early and long-term benefits with clopidogrel were demonstrated in the Clopidogrel for the Reduction of Events during Observation (CREDO) trial, in which patients were randomized to a loading dose of clopidogrel 3 to 24 hours before PCI and then to continued maintenance therapy with clopidogrel beyond the first month after the procedure, compared with patients who were not administered a loading dose and were treated with clopidogrel for only 28 days after PCI.[39] Overall, patients randomized to early and sustained clopidogrel treatment had a 26.9% reduction in the risk of death, MI, or stroke. It is important to note that there appeared to be continued benefit for long-term treatment with clopidogrel throughout the treatment period of 1 year.[39] As was seen in the diabetic subgroup of the PCI-CURE substudy, the relative benefit of clopidogrel in diabetic patients was comparable, but numerically smaller, than that seen in nondiabetic patients (11.2% RRR, 95% CI 46.2% to −46.8 versus 32.8% RRR, 95% CI 51.6%-6.8%).[39]

Higher loading (600 mg) and maintenance doses (150 mg daily for 6 days) of clopidogrel were compared with standard doses of clopidogrel in patients after ACS in the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial (see also **Chapter 21**).[23] Although double-dosing did not reduce the risk of 30-day CV events in the overall study population (HR 0.94, 95% CI 0.83-1.06), the higher-dose regimen was associated with a reduced risk of CV death, MI, or stroke (HR 0.86, 95% CI 0.74-0.99) in the cohort of patients who underwent PCI. However, the higher dose of clopidogrel also increased the risk of major bleeding by 42% (HR 1.42, 95% CI 1.09-1.83). There was no evidence of heterogeneity by DM status for the primary efficacy endpoint (P for interaction = 0.32).[23]

The use of dual antiplatelet therapy in stable secondary prevention and high-risk primary prevention was evaluated in the CHARISMA trial.[40] Overall, clopidogrel did not reduce the risk of CV events when compared with placebo, and there was no evidence of interaction by DM status. In a post hoc analysis, the subgroup of patients with prior MI, ischemic stroke, or symptomatic PAD showed a 17% RRR with dual antiplatelet therapy.[41] In contrast, there was no clear benefit and an increased risk of bleeding in high-risk patients in the absence of established vascular disease (**Fig. 16-5**). Of note, the primary prevention cohort was enriched with diabetic patients based on the entry criteria. Therefore the results of the CHARISMA trial do not support the use of dual antiplatelet therapy in diabetic patients for primary prevention, but ongoing trials may demonstrate a benefit for more

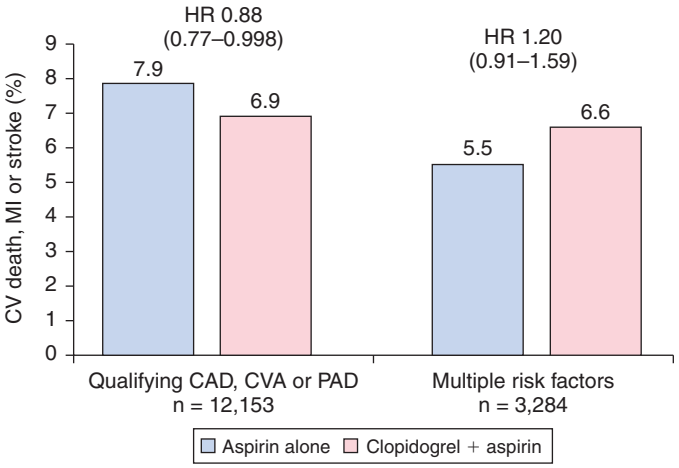


FIGURE 16-5 The relative effect (HR, 95% CI) of clopidogrel versus placebo in patients with symptomatic atherosclerotic disease or multiple risk factors in the CHARISMA trial. In subgroup analyses, clopidogrel reduced the risk of CV death, MI, or stroke in patients with symptomatic atherosclerotic disease, but not in patients who only had multiple risk factors in the absence of symptoms. The diabetic population was enriched in the latter group.[40] *(Modified from Bhatt DL, Fox KA, Hacke W, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events,* N Engl J Med *354:1706-1717, 2006.)*

prolonged dual antiplatelet therapy in patients with established vascular disease.

Another area of ongoing investigation is the optimal duration of dual antiplatelet therapy after PCI (see also **Chapter 17**). Several studies have demonstrated that there is an increased risk of adverse outcomes after discontinuation of clopidogrel.[42] In a study of 749 patients with DM who underwent stenting, the use of more prolonged dual antiplatelet therapy was associated with a reduced risk of death or MI in patients after bare metal stent placement ($P = 0.01$) and a reduced risk of death in patients with a drug-eluting stent (DES) ($P = 0.03$).[43] However, many of the analyses to date have been observational in design, and therefore it is plausible that the results might be explained by confounding. In particular, clopidogrel is often discontinued in the setting of bleeding or surgery, which may independently place a patient at increased risk of CV events.

To date, only a small number of studies have addressed the optimal duration of dual antiplatelet therapy with a randomized design. The Prolonging Dual Antiplatelet Treatment after Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial randomized 2013 patients who had undergone PCI to dual antiplatelet therapy for a period of 6 versus 24 months.[44] The incidence of CV death, MI, or stroke was observed to be similar in both treatment arms (10.1% versus 10.0%, $P = 0.92$), whereas the incidence of bleeding (Bleeding Academic Research Consortium [BARC] type 2, 3, and 5) was higher for patients who continued dual antiplatelet therapy for 24 months (7.4% versus 3.5%, $P < 0.001$). Similar findings were seen in two trial populations that were composed of 2701 patients in Korea who were randomized to aspirin alone versus continued dual antiplatelet therapy 12 months after PCI.[45] Although the study was underpowered because of a low event rate, more prolonged dual antiplatelet therapy failed to demonstrate any signal toward clinical efficacy.[45] In a second study underpowered to assess noninferiority, a similar lack of efficacy was demonstrated for dual-antiplatelet therapy beyond

6 months in patients undergoing placement of a DES.[46] The efficacy and safety of prolonged dual antiplatelet therapy beyond 12 months are currently undergoing evaluation in the larger Dual Antiplatelet Therapy (DAPT) Study (clinicaltrials.gov NCT00977938). The DAPT trial is enrolling patients after PCI and then randomizing those patients who are event free after 12 months to an additional 18 months of treatment with a thienopyridine versus placebo.

Clopidogrel Response Variability

There exists significant interindividual variability in pharmacodynamic response to clopidogrel.[47] In turn, diabetic patients with an inadequate response to clopidogrel are at increased risk of CV events.[48] The estimated prevalence of individuals with an inadequate response to clopidogrel varies considerably depending on the applied definitions, type of assay, dose of clopidogrel, and patient population. In patients undergoing elective PCI, it has been described that approximately 31% of individuals will have less than 10% inhibition of platelet aggregation (IPA) at 24 hours as measured by light transmission aggregometry after a 300-mg loading dose of clopidogrel.[49] It is important to note there is evidence that the prevalence of clopidogrel hyporesponders is higher in patients with DM and is highest in patients requiring insulin therapy (see **Fig. 16-4**).[37] In the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) trial, individuals with DM had higher baseline platelet reactivity, and almost two thirds of diabetic patients were demonstrated to have an inadequate response to clopidogrel.[36] Higher baseline platelet reactivity and diminished response to clopidogrel may therefore in part explain the persistent risk of CV events that is observed in diabetic patients.

It remains unknown whether specific genetic, cellular, and clinical causes may contribute to the higher prevalence of clopidogrel hyporesponders in diabetic patients. Regardless of DM status, several studies have demonstrated that clopidogrel-treated patients with at least one copy of a reduced-function *CYP2C19* allele have an increased risk of CV events after undergoing PCI[50]; however, genotype appears to explain only a small fraction of observed interpatient variability.[51] In diabetic patients, in the setting of excess insulin, there is evidence to suggest that platelets develop insulin resistance leading to upregulation of the P2Y12 receptor[52] and heightened platelet reactivity.[53] Additional cellular factors that may contribute to the observed attenuation in response in diabetic patients include alterations in calcium metabolism,[54] increased ADP exposure, and accelerated platelet turnover.[55]

Because patients with DM may have upregulation of the P2Y12 receptor, there has been interest in using a higher dose of clopidogrel to help overcome pharmacodynamic resistance. In the OPTIMUS trial, the use of 150 mg of clopidogrel daily resulted in greater IPA than the 75-mg dose in diabetic patients with poor pharmacodynamic response to clopidogrel. However, despite the use of the 150-mg maintenance dose, a substantial fraction of diabetic patients continued to have high post-treatment platelet reactivity. Similar findings were observed in Gauging Responsiveness with a VerifyNow P2Y12 Assay—Impact on Thrombosis and Safety (GRAVITAS) (see also **Chapter 17**),[56] a trial of 2214 patients with high on-treatment platelet reactivity with clopidogrel after placement of a DES; the patients were randomized to high-dose (600-mg loading dose then 150 mg daily) or standard-dose (75 mg daily) clopidogrel. The prevalence of high on-treatment platelet reactivity was observed to be higher among diabetic patients, and as a consequence almost half the patients who were determined to have high on-treatment platelet reactivity had diabetes. Although higher doses of clopidogrel reduced the in vitro prevalence of pharmacodynamic clopidogrel hyporesponders, clopidogrel 150 mg daily failed to reduce the risk of CV events as compared with standard dosing in these high-risk patients. Therefore there are no prospective data that support routine platelet function testing at the present time.

Prasugrel

Prasugrel is a third-generation thienopyridine that irreversibly binds to the P2Y12 receptor to inhibit platelet activation and aggregation. Although the active metabolites of both clopidogrel and prasugrel have similar affinity for the P2Y12 receptor in vitro, prasugrel achieves more rapid and more potent IPA than clopidogrel. It is hypothesized that this is because of its more efficient pathway of drug metabolism and activation.[57] Clopidogrel requires two separate CYP-dependent oxidative steps to form its active metabolite, and most of the prodrug is metabolized by esterases that shunt the drug toward a dead-end inactive pathway. In contrast, esterases assist with activation of the prasugrel prodrug, and prasugrel is oxidized to its active metabolite in a single CYP-dependent step.[58] After a 60-mg loading dose, prasugrel has been shown to significantly inhibit platelets within 30 minutes of ingestion.[57] In contrast, a 300-mg loading dose of clopidogrel requires approximately 6 hours to achieve steady-state, and a 600-mg loading dose takes approximately 2 hours to demonstrate clinically relevant antiplatelet effects. In addition to its enhanced potency, prasugrel demonstrates diminished interpatient variability as compared with clopidogrel.[47]

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 enrolled 13,608 patients with ACS and undergoing PCI to prasugrel (60-mg loading dose, 10 mg daily) or clopidogrel (300-mg loading dose, 75 mg daily) on a background of aspirin (see also **Chapter 21**).[59] After a median of 14.5 months, prasugrel significantly reduced the risk of CV death, MI, or stroke by 19% as compared with clopidogrel (HR 0.81, 95% CI 0.73-0.90). Furthermore, prasugrel significantly reduced the risk of MI (9.7% versus 7.4%, $P < 0.001$), urgent target-vessel revascularization (3.7% versus 2.5%, $P < 0.001$), and stent thrombosis (2.4% versus 1.1%, $P < 0.001$).[59] The benefit of prasugrel appeared early, and landmark analyses demonstrated that the benefit appeared to persist over time. Although the incidence of bleeding was low, prasugrel significantly increased the risk of non–coronary artery bypass graft (CABG) surgery–related TIMI major bleeding by 32%, including a significant increase in the risk of life-threatening and fatal bleeding.[60] Subsequent post hoc analyses demonstrated the patients with a history of stroke or TIA do not appear to benefit from prasugrel and may incur harm from more potent antiplatelet therapy. In addition, a net clinical benefit was not observed in patients aged older than 75 years or weighing less than 60 kilograms.

Of interest, the balance between efficacy and safety for prasugrel compared with clopidogrel appeared most favorable in diabetic patients enrolled in the TRITON-TIMI 38 trial with DM.[61] Of the 3146 patients with DM, prasugrel

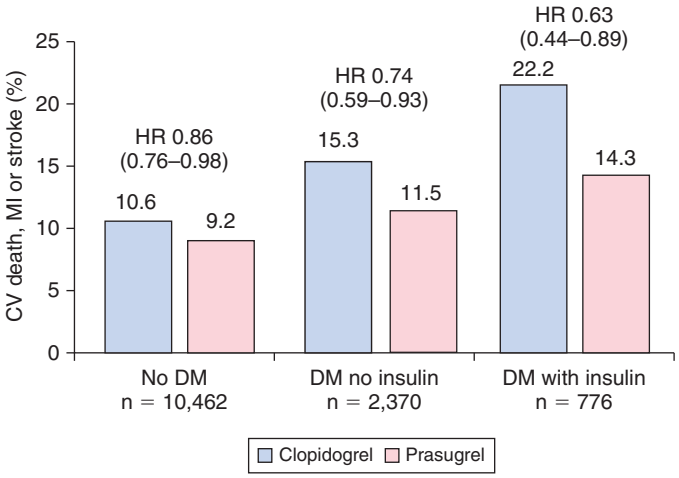


FIGURE 16-6 Clinical events and relative benefit (HR, 95% CI) of prasugrel versus clopidogrel for patients without DM, diabetic patients not treated with insulin, and insulin-treated diabetic patients in the TRITON-TIMI 38 trial. The relative benefit of prasugrel versus clopidogrel appeared to be enhanced in diabetic patients, and further benefit was observed in those patients requiring insulin therapy.[61] *(Modified from Wiviott SD, Braunwald E, Angiolillo DJ, et al: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel—Thrombolysis in Myocardial Infarction 38,* Circulation *118:1626-1636, 2008.)*

significantly reduced the risk of CV death, MI, or stroke by 30% (HR 0.70, 95% CI 0.58-0.85, $P<0.001$, P interaction = 0.09) and this benefit was further increased to 37% in insulin-treated patients (HR 0.63, 95% CI 0.44–0.89, **Fig. 16-6**).[61] Prasugrel reduced the risk of MI by 40% in diabetic patients (HR 0.60, 95% CI 0.48-0.76), as opposed to by 18% in nondiabetic patients (HR 0.82, 95% CI 0.72-0.95, P interaction = 0.02). Also, prasugrel reduced the risk of stent thrombosis in the overall diabetic cohort (3.6% versus 2.0%, HR 0.52, 95% CI 0.33-0.84), and this benefit was further enhanced in diabetic patients requiring insulin (5.7% versus 1.8%, HR 0.31, 95% CI 0.12-0.77). Although diabetic patients had a higher absolute rate of bleeding, prasugrel did not appear to substantially increase the risk of major bleeding as compared with clopidogrel in this high-risk patient group (2.6% versus 2.5%, HR 1.06, 95% CI 0.66-1.69). Because of the higher event rate and greater benefit of prasugrel in insulin-treated patients, the absolute risk reduction in CV events with prasugrel was 8% indicating that only 13 insulin-treated diabetic patients would need to be treated to prevent one ischemic event, contrasted with a number-needed-to-treat of 26 for DM patients not on insulin. The observations from the diabetic subgroup of the TRITON-TIMI 38 trial therefore support the hypothesis that the achieved degree of platelet reactivity is an important predictor of outcome. Because individuals with DM have higher baseline platelet reactivity and diminished pharmacodynamic response to clopidogrel, it is plausible that diabetic patients derive enhanced benefit from this more potent antiplatelet therapy that is able to attain lower levels of on-treatment platelet reactivity.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial was a two-phase study of 201 patients undergoing PCI that compared the pharmacodynamic response to prasugrel (60-mg loading dose, 10 mg daily) with higher-dose clopidogrel (600-mg loading dose, 150 mg daily).[57] Prasugrel achieved greater IPA as compared with higher-dose clopidogrel in both the loading dose and maintenance dose phases. The rate of patients who were hyporesponsive to clopidogrel (IPA ≤20% in response to 20 μM ADP) was higher in diabetic patients than nondiabetic patients at all timepoints. In contrast, no hyporesponders were observed for patients on prasugrel at 6 hours regardless of diabetes status.[57] Consistent findings were observed in the OPTIMUS-3 trial, which exclusively enrolled patients with DM.[62] In OPTIMUS-3, individuals with DM and coronary artery disease (CAD) were randomized to prasugrel (60-mg loading dose, 10 mg daily) or clopidogrel (600-mg loading dose, 150 mg daily) over two 1-week treatment periods separated by a 2-week washout. Prasugrel achieved greater platelet inhibition than high-dose clopidogrel at 4 hours after a loading dose. This difference was maintained throughout the loading dose and maintenance phase (from 1 hour through 7 days, $P<0.001$). Prasugrel reduced the number of diabetic patients with an inadequate response to thienopyridine therapy as compared with high-dose clopidogrel.[62]

After the publication of the TRITON-TIMI 38 trial findings, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial compared the long-term efficacy of prasugrel (10 mg daily) versus clopidogrel (75 mg daily) in 7243 patients with ACS who were managed medically without coronary revascularization (see also **Chapter 21**).[63] A lower dose of prasugrel (5 mg daily) was used in patients who weighed less than 60 kg or were older than 75 years. The primary analysis was restricted to patients younger than 75 years. In this patient group, prasugrel did not significantly reduce the risk of CV death, MI, or stroke as compared with clopidogrel (HR 0.91, 95% CI 0.79-1.05). The findings were consistent in the subset of 2811 patients with DM (HR 0.90, 95% CI 0.73-1.09, P interaction = 0.71). The prespecified analysis of first or recurrent ischemic events (all components of the primary endpoint) suggested a lower risk for prasugrel among patients under the age of 75 years (HR 0.85; 95% CI 0.72 to 1.00; $P=0.04$). Rates of severe and intracranial bleeding were similar in the two groups in all age groups.[63] Therefore the findings of the TRILOGY ACS trial do not support the use of prasugrel in patients who are managed without coronary revascularization.

The 2012 Focused Update to the ACCF/AHA Guidelines for the Management of Patients with non–ST-elevation ACS offers a class I recommendation for the use of clopidogrel, prasugrel, or ticagrelor (see later) on a background of aspirin in patients with unstable angina (UA) or non–ST-segment myocardial infarction (NSTEMI) who are undergoing PCI, with no distinction in the recommendations with regard to drug of choice based on DM status (see also **Chapter 21**).[24] If prasugrel is used, it should be given promptly and no later than 1 hour after PCI once the coronary anatomy is defined and the decision is made to proceed with PCI (see also **Chapters 17** and **22**). Based on the findings from TRITON-TIMI 38, prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (TIA). In patients over the age of 75 years, the use of prasugrel is generally not recommended but may be considered in high-risk patients such as those with DM. A lower dose of 5 mg daily can be considered in patients over the age of 75 or who weigh less than 60 kg. Prasugrel should be continued for at least 12 months in ACS patients who undergo PCI. Earlier discontinuation of

a P2Y12 receptor inhibitor can be considered in patients in whom the anticipated morbidity from bleeding exceeds its benefits.

Ticagrelor

Ticagrelor is the first reversibly binding oral P2Y12 receptor antagonist.[64] It is a nonthienopyridine and does not require metabolism to form its active metabolite. It has been shown to bind the P2Y12 receptor with a noncompetitive binding mechanism toward ADP. Similar to prasugrel, ticagrelor demonstrates rapid onset of action and decreased interpatient variability as compared with clopidogrel. Because of an elimination half-life of 7 hours and its reversible binding characteristics, it is administered twice daily. However, its antiplatelet effects have been shown to extend to approximately 120 hours.[64] Although it is more potent than clopidogrel, its ability to inhibit platelet aggregation is roughly equivalent to that of clopidogrel at 24 hours after drug discontinuation because of its faster offset kinetics. Ticagrelor may therefore be less likely than clopidogrel to increase the risk of bleeding in patients who require surgery 48 to 120 hours after the last dose.[64]

The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial evaluated the safety and efficacy of ticagrelor in 18,624 patients across the spectrum of ACS (see also **Chapter 21**).[65] Patients were randomized to clopidogrel (300- to 600-mg loading dose, 75 mg daily) or ticagrelor (180-mg loading dose, 90 mg daily). At 12 months, ticagrelor reduced the risk of vascular death, MI, or stroke by 16% (HR 0.84, 95% CI 0.77-0.92), as compared with clopidogrel. In addition, ticagrelor reduced the risk of death from vascular causes (4.0% versus 5.1%, $P=0.001$) and all-cause mortality (4.5%, versus 5.9% with clopidogrel, $P<0.001$), but increased the risk of non–CABG-related Thrombolysis in Myocardial Infarction (TIMI) major bleeding by 25% ($P=0.03$). Of the P2Y12 inhibitors that have been evaluated to date, ticagrelor is the only drug to have demonstrated a mortality benefit across the spectrum of ACS. However, ticagrelor did not increase the risk of fatal bleeding ($P=0.66$) or CABG-related major bleeding ($P=0.32$).

The relative benefit of ticagrelor appeared to be comparable in diabetic and nondiabetic patients in PLATO, although the absolute benefits were greater in insulin-treated diabetic patients.[66] Ticagrelor reduced the risk of vascular death, MI, or stroke by 12% in diabetic patients (HR 0.88, 95% CI 0.76-1.03) versus 17% in nondiabetic patients (HR 0.83, 95% CI 0.74-0.92, P interaction $=0.49$; **Fig. 16-7**). Similarly, in diabetic patients, ticagrelor reduced the risk of all-cause mortality (HR 0.82, 95% CI 0.66-1.01) and stent thrombosis (HR 0.65, 95% CI 0.36-1.17) to an extent that was consistent with the overall cohort. Ticagrelor tended to increase non–CABG-related PLATO major bleeding in both diabetic and nondiabetic patients (HR 1.13, 95% CI 0.86-1.49; HR 1.22, 95% CI 1.01-1.46, respectively, P interaction $=.69$). There was no heterogeneity in the efficacy or safety of ticagrelor with regard to patients who were or were not treated with insulin.[66]

If diabetic patients indeed derive enhanced benefit from more potent antiplatelet therapy after ACS, it is unclear why these findings were not observed in the PLATO trial. In patients who are hyporesponsive to clopidogrel, switching to ticagrelor has been shown to inhibit platelet aggregation to the same extent as it does when clopidogrel-responsive patients are treated with ticagrelor.[67] In this same study,

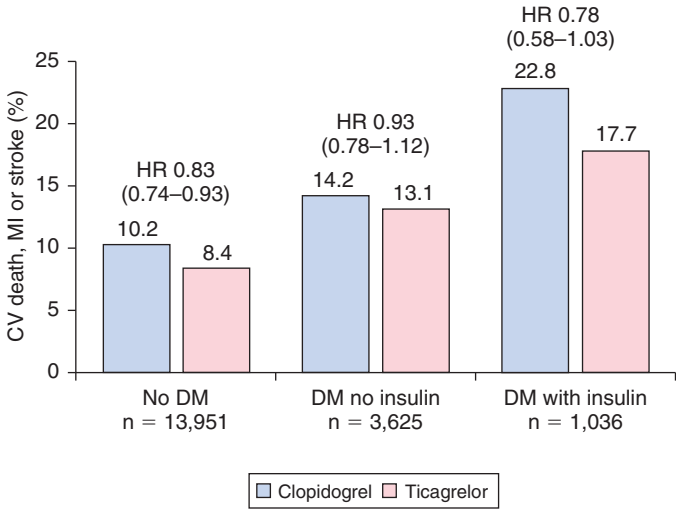


FIGURE 16-7 Clinical events and comparative efficacy (HR, 95% CI) of ticagrelor versus clopidogrel for patients without DM, diabetic patients not treated with insulin, and patients with diabetes treated with insulin in the PLATO trial. The absolute benefit of ticagrelor appeared largest in diabetic patients treated with insulin, although the relative benefits were similar in all three groups.[66] *(Modified from James S, Angiolillo DJ, Cornel JH, et al: Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial,* Eur Heart J *31:3006-3016, 2010.)*

almost all patients treated with ticagrelor (25% of whom had diabetes) achieved platelet reactivity levels below the threshold that has been shown to be associated with an increased risk of ischemic events regardless of their clopidogrel response status.[67]

There are limited head-to-head data to compare the pharmacodynamic or clinical efficacy of prasugrel with that of ticagrelor. In a study of 44 patients with ACS (23% of whom had DM) and high on-treatment platelet reactivity on clopidogrel, patients were randomized in a double-blind crossover design to either ticagrelor 90 mg twice daily or prasugrel 10 mg daily without a loading dose for 15 days before crossing over to the alternate therapy.[68] At the end of the two treatment periods, ticagrelor achieved a greater degree of platelet inhibition than prasugrel ($P<0.001$). Both drugs were effective at reducing platelet reactivity below the predefined threshold for poor response.[68] It remains unknown whether the two drugs would demonstrate similar clinical efficacy if compared in a large-scale head-to-head clinical trial or if similar pharmacodynamic effects would have been observed if a loading dose of the drugs had been administered.

Unlike with prasugrel, the benefit of ticagrelor has not been directly assessed in a dedicated trial population of patients managed without PCI. However, in the PLATO trial, ticagrelor reduced the risk of vascular death, MI, or stroke in patients who were intended to be managed noninvasively (HR 0.85, 95% CI 0.73-1.00, $P=0.04$), of whom 29% eventually underwent PCI.[69] Ticagrelor is the first of the two novel P2Y12 antagonists to be evaluated in a population of patients with stable CAD. The ongoing Prevention with Ticagrelor of Secondary Thrombotic Events in High-Risk Patients with Prior Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction (PEGASUS-TIMI) 54 trial (clinicaltrials.gov NCT01225562) has enrolled intermediate- to high-risk individuals with a history of MI in the past 1 to 3 years to one of two doses of ticagrelor (60 mg or 90 mg twice daily) or placebo on a background of low-dose aspirin.[69a] The trial will

directly address the clinical efficacy of ticagrelor in patients with stable CAD and will also help to assess the optimal duration of dual antiplatelet therapy in patients after MI. As well, The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial is evaluating the efficacy and safety of ticagrelor (90 mg twice daily) in patients with type 2 diabetes mellitus and either a documented history of obstructive coronary artery disease or prior coronary revascularization (clinicaltrials.gov NCT01991795).

OTHER ANTIPLATELET MEDICATIONS

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor that raises cyclic adenosine monophosphate (cAMP) levels in platelets and vascular smooth muscle cells, leading to inhibition of platelet activation and arteriolar vasodilation.[70] When cilostazol was added to a background of dual antiplatelet therapy, nonrandomized studies demonstrated that this agent appeared to reduce the risk of stent thrombosis[71,72] and ischemic events,[72,73] without a significant increase in bleeding. Thus far, randomized trials of triple antiplatelet therapy in patients after PCI have yielded conflicting results, although most trials have been underpowered for clinical outcomes (see also **Chapter 17**).[74] In the Efficacy of Cilostazol on Ischemic Complications after Drug-Eluting Stent Implantation (CILON-T) trial, the addition of cilostazol failed to reduce the risk of cardiac death, nonfatal MI, ischemic stroke, or target lesion revascularization in patients after DES implantation (8.5% versus 9.2%, $P=0.74$), despite achieving a reduction in platelet reactivity.[74] In contrast, in a second trial of patients after ACS undergoing PCI, cilostazol reduced the risk of cardiac death, nonfatal MI, stroke, or target vessel revascularization (10.3% versus 15.1%, $P=0.011$) when added to aspirin and clopidogrel.[75] In the latter study, the benefit of cilostazol appeared to be enhanced in patients with high-risk clinical or angiographic features, including DM (n = 263, 9.9% versus 18.9%, HR 0.47, 95% CI 0.23-0.96).[75]

These findings are supported by pharmacodynamic data that have shown that cilostazol enhances inhibition of P2Y12 signaling in diabetic patients.[76] Cilostazol combined with standard-dose clopidogrel reduces platelet reactivity to a greater extent than clopidogrel 150 mg daily in patients with type 2 DM.[77] The greater pharmacodynamic effect of cilostazol in diabetic patients was observed regardless of whether or not patients carried genetic polymorphisms that have been shown to influence response to clopidogrel.[77] These findings may in part explain the ability of cilostazol to reduce the risk of ischemic events in high-risk patients. To that end, the antiplatelet effects of cilostazol appear to be enhanced in diabetic patients[78] and patients with high on-treatment platelet reactivity.[79,80]

In addition to its antiplatelet effects, cilostazol is hypothesized to exert pleiotropic effects including inhibition of neointimal hyperplasia. Supporting this concept, a systematic review that combined data from 23 randomized trials of cilostazol suggested that it may reduce the risk of in-stent restenosis (RR 0.60, 95% CI 0.49-0.73) and need for repeat revascularization (RR 0.69, 95% CI 0.55-0.86) without a significant increase in bleeding (RR 0.71, 95% CI 0.43-1.16) in patients after PCI.[81] In a dedicated trial of diabetic patients receiving a DES, the addition of cilostazol to aspirin and clopidogrel reduced angiographic restenosis and extent of late luminal loss, thereby leading to a lower rate of target lesion revascularization at 9 months as compared with dual antiplatelet therapy alone.[82] Although the study was underpowered for clinical events, major adverse cardiac events tended to be lower in the triple than in the dual antiplatelet therapy group (3.0% versus 7.0%, $P=0.066$).[82] However, the use of cilostazol is limited by a high frequency of side effects including headache, GI disturbance, and palpitations. Larger, more definitive studies of cilostazol are therefore needed before it can be routinely used as an adjunct to dual antiplatelet therapy after coronary stenting.

Dipyridamole

Dipyridamole exhibits a number of properties that contribute to platelet inhibition and vasodilation. Dipyridamole inhibits thromboxane synthase leading to reduced TXA_2 production and thereby reduced platelet activation.[83] It inhibits adenosine deaminase and cellular reuptake of adenosine into platelets, erythrocytes, and endothelial cells causing extracellular adenosine levels to rise.[83] Dipyridamole is also a phosphodiesterase inhibitor leading to higher cAMP and cyclic guanosine monophosphate (cGMP) levels within platelets and endothelial cells and thereby blocking response to ADP via the P2Y12 receptor and enhancing nitric oxide signaling.[83,84]

Although there are limited data to support the use of dipyridamole in patients with CHD, its use has been extensively studied in patients with cerebrovascular disease in combination with aspirin. In the European Stroke Prevention Study (ESPS), the combination of aspirin (330 mg) and dipyridamole (75 mg) three times daily reduced the risk of all-cause mortality or stroke by 33.5% compared with placebo in patients with a recent stroke or TIA.[85] Moreover, the benefit appeared to be further enhanced in diabetic versus nondiabetic patients (48% versus 32%, respectively).[86] Furthermore, it appears that the effects of dipyridamole and aspirin are additive.[87] In patients with recent stroke or TIA, the combination of dipyridamole (400 mg daily) and aspirin (50 mg daily) reduced the risk of stroke by 37% compared with placebo, whereas dipyridamole alone reduced the risk of stroke by 16% and aspirin alone by 18%.[87] In the open-label European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), the combination of aspirin plus dipyridamole (200 mg twice daily) reduced the risk of CV death, MI, stroke, or major bleeding by 20% (HR 0.80, 95% CI 0.66-0.98), as compared with aspirin alone (30 to 325 mg daily) in patients with a history of an acute cerebrovascular event.[88] An increased frequency of headache contributed to a higher rate of discontinuation in the dipyridamole group.[88] Currently there is no role for dipyridamole for the purpose of reduction of coronary risk.

PROTEASE-ACTIVATED RECEPTOR 1 ANTAGONISTS

Vorapaxar

Thrombin stimulates platelet activation via protease-activated receptor 1 (PAR-1), the major thrombin receptor on the platelet cell surface. Although extensive research has been directed toward the ADP-dependent P2Y12 receptor, thrombin is the most potent platelet agonist.[89] Because aspirin and clopidogrel do not interfere with

PAR-1–dependent platelet activation, patients on standard dual antiplatelet therapy remain at risk of recurrent CV events via alternate pathways of platelet activation.

Vorapaxar is a competitive and selective antagonist of PAR-1 that acts by binding at or near the tethered ligand binding site.[89] Because PAR-1 receptor antagonists selectively interfere with thrombin-mediated platelet activation without disrupting the coagulation cascade or ADP-dependent platelet activation, it was hypothesized that PAR-1 receptor antagonists might reduce the risk of ischemic events without significantly increasing the risk of bleeding. This hypothesis was supported by phase II studies that suggested trends toward efficacy with increasing doses of vorapaxar and without a significant increase in major bleeding.[90]

Vorapaxar was subsequently evaluated in two large-scale clinical trials of patients with stable atherosclerotic disease or ACS, the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA2°P-TIMI 50) and the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndrome (TRA-CER), respectively. In January 2011, the joint Data and Safety Monitoring Board for the two trials reported an excess in intracranial hemorrhage in patients with a history of stroke. As a consequence, the study drug was discontinued in the TRA2°P-TIMI 50 trial for patients with a history of stroke, but the trial continued to completion in patients with a history of MI or PAD. The TRA-CER trial was stopped prematurely after reaching its prespecified number of primary endpoints.

In the 26,449 patients with stable atherosclerotic disease enrolled in the TRA2°P-TIMI 50 trial, vorapaxar (2.5 mg daily) significantly reduced the risk of CV death, M, or stroke by 13% and the risk of CV death, MI, stroke, or urgent coronary revascularization by 12% (HR 0.88, 95% CI 0.82-0.95) as compared with placebo during a median follow-up of 2.5 years.[91] Although vorapaxar reduced the risk of recurrent CV events, vorapaxar increased the risk of moderate or severe bleeding by 66% (HR 1.66, 95% CI 1.43-1.93), including a significant increase in the risk of intracranial hemorrhage. The rate of fatal bleeding was not significantly increased in the vorapaxar group. The efficacy and safety of vorapaxar were consistent in patients with or without DM (P interaction = 0.61 for CV death, MI, or stroke; P interaction = 0.79 for GUSTO moderate or severe bleeding). No heterogeneity was observed on the basis of background thienopyridine use.

The balance between efficacy and safety appeared to be most favorable for vorapaxar in patients with a history of MI more than 1 month before randomization in the TRA°2P-TIMI 50 trial.[92] Of the 17,779 patients within this prespecified subgroup, vorapaxar significantly reduced the risk of CV death, MI, or stroke by 20% (HR 0.80, 95% CI 0.72-0.89), including a 21% reduction in the risk of MI (HR 0.79, 95% CI 0.70-0.89) and a 34% reduction in the risk of ischemic stroke (HR 0.66, 95% CI 0.48-0.89). Moderate or severe bleeding remained more common in patients treated with vorapaxar as compared with patients on placebo (HR 1.61, 95% CI 1.31-1.97). Within this subgroup of patients, intracranial hemorrhage was infrequent and not statistically increased for patients on vorapaxar (0.6% versus 0.4%, P = 0.076).[92]

Despite an observed trend toward efficacy, vorapaxar was not superior to placebo for the management of patients with ACS in the TRA-CER trial.[93] Vorapaxar (40-mg loading dose, 2.5 mg daily) did not significantly reduce the risk of the primary endpoint of CV death, MI, recurrent ischemia with hospitalization, or urgent coronary revascularization (HR 0.92, 95% CI 0.85-1.017) in patients after ACS. Vorapaxar did reduce the key secondary endpoint of CV death, MI, or stroke by 11% compared with placebo (HR 0.89, 95% CI 0.81-0.98), including a 12% reduction in MI (HR 0.88, 95% CI 0.79-0.98). Consistent with the findings from the TRA°2P-TIMI 50 trial, vorapaxar increased the risk of GUSTO moderate or severe bleeding (HR 1.35, 95% CI 1.16-1.58) and intracranial hemorrhage (HR 3.39, 95% CI 1.78-6.45) in patients after ACS.

Atopaxar

Atopaxar (E5555) is a second orally active, reversible, small molecule inhibitor that selectively inhibits PAR-1 activation by binding at or near the tethered ligand binding site. Although vorapaxar and atopaxar share similarities, vorapaxar exhibits a much longer half-life (165 to 311 hours) and achieves 50% recovery of platelet function at 4 weeks after treatment discontinuation. In contrast, atopaxar has an approximate plasma half-life of 22 to 26 hours.[89]

The phase II Lessons from Antagonizing the Cellular Effects of Thrombin (LANCELOT) program evaluated the safety tolerability of atopaxar in patients after ACS or with stable CAD.[89,94,95] In patients after ACS, atopaxar significantly reduced Holter-detected ischemia without a clear increase in major bleeding compared with placebo.[89] Similar findings were observed in patients with CAD, including a nonsignificant trend toward reduced ischemic events.[94] In a focused platelet function substudy, atopaxar achieved rapid and sustained platelet inhibition via the PAR-1 receptor.[89,94] Although the drug was generally well tolerated, liver transaminase elevation and relative QTc prolongation were observed with the highest doses of atopaxar. To date, atopaxar has not been evaluated in phase III testing.

FUTURE DIRECTIONS

As the prevalence of DM continues to grow, there will be an urgent need to develop therapies that may help to attenuate CV risk in this high-risk population. In addition to the antiplatelet drugs reviewed in this chapter, several novel antiplatelet drugs remain in development. Cangrelor is a direct-acting and reversible intravenous P2Y12 receptor inhibitor whose use has been studied in the setting of PCI[96,97] and as a bridge to surgery for patients off oral P2Y12 inhibition.[98] Picotamide inhibits TXA_2 synthase and TXA_2 receptors and has been proposed as an alternative to aspirin.[99] Because the drug blocks TXA_2 through pathways independent of COX-1, it may offer enhanced benefit to diabetic patients who respond inadequately to aspirin.[99] As more potent or alternate antiplatelet therapies undergo clinical evaluation, continued emphasis will need to be placed on achieving the optimal balance between efficacy and safety.

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17 Role of Percutaneous Coronary Intervention in Patients with Diabetes

Baris Gencer and Marco Roffi

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Diabetes mellitus is a major risk factor for cardiovascular disease affecting multiple vascular territories. At the cardiac level, it is associated with a risk of coronary artery disease (CAD) equivalent to 15 years of ageing.[1–3] Although coronary revascularization has definitively shown a benefit in terms of major cardiovascular event (MACE) reduction,[4] especially in acute coronary syndromes (ACSs), several studies have reported worse outcomes associated with revascularization in diabetic patients than in those without diabetes.[5–13]

The aims of coronary revascularization in stable CAD are to improve prognosis and symptoms. The importance of optimal medical treatment—independent of the revascularization modality—is especially true for the diabetic patient population. In the current context of an increasing prevalence of diabetes, particular attention is needed in the development of new strategies in the field of adjuvant pharmacologic therapies and new generations of drug-eluting stents (DESs).[14–16] Despite all the advances in the field, patients with diabetes undergoing revascularization—both surgical and through percutaneous coronary intervention (PCI)—continue to have worse outcomes compared with nondiabetic counterparts.[17–19]

For patients with diabetes, assessment of several clinical parameters, such as coronary anatomy, complexity of lesions, clinical presentation, left ventricular function, comorbidities, and patient preference, may help to determine the best revascularization option (**Fig. 17-1**).[20] The European myocardial revascularization guidelines recommend revascularization in all stable patients with diabetes and extensive CAD (Class I, level of evidence A).[21] The type of revascularization is discussed in this section, mainly for patients with stable CAD; revascularization for patients with diabetes in the setting of ACS is covered in **Chapter 22**.

SPECIFIC CHARACTERISTICS OF DIABETES-ASSOCIATED ATHEROTHROMBOSIS

Diabetic patients constitute a subgroup of patients at increased risk of unfavorable outcomes after PCI as a result of more severe and extensive CAD, as well as a higher rate of restenosis.[19,22,23] In addition, diabetic patients are characterized by prothrombotic and proinflammatory states induced by a variety of metabolic disturbances that may lead, among other complications, to increased plaque vulnerability, platelet reactivity, and thrombotic complications after PCI. The EVASTENT registry, with 1731 patients treated with DESs, reported that patients with diabetes and multivessel CAD had the highest risk of stent thrombosis (ST)—4.3% at 1 year.[24]

Hyperglycemia, insulin resistance, and oxidative stress are the major abnormalities of regulatory mechanisms that contribute to the dysfunction of extracellular and intracellular molecular pathways of endothelial cells, platelets, and blood coagulant factors (for details, see **Chapters 9** and **10**).[25,26] In the bare-metal stent (BMS) era, the most evident adverse effect of diabetes after PCI was the increased prevalence of restenosis[14,16] with DESs—at least, first-generation DESs. Although diabetes remains a risk factor for increased risk of restenosis, an increased risk of ST has become a greater consideration in the context of diabetes.[27] Accordingly, diabetes has been identified as an independent predictor of ST in a variety of studies addressing the use of first-generation DESs (**Fig. 17-2**).[20]

METHODOLOGIC CONSIDERATIONS RELATED TO PERCUTANEOUS CORONARY INTERVENTION TRIALS IN DIABETES

A large number of PCI trials have been performed, enrolling nondiabetic and diabetic patients and using composite endpoints, such as death, myocardial infarction (MI), stroke, target vessel MI, repeat revascularization, target vessel revascularization (TVR), target lesion revascularization (TLR), stent restenosis, in-stent late lumen loss, and ST. The angiographic intermediate endpoints, such as late lumen loss and percent diameter stenosis, both in-stent and in-segment, have been well accepted as primary endpoints for the design of stent trials.[28] Composite endpoints are widely used by investigators to decrease the needed sample size and the duration of follow-up and are justified with the rationale that treatment would have comparable directional impact across the spectrum of components incorporated into the key composite endpoints.[29] The interpretation of comparative

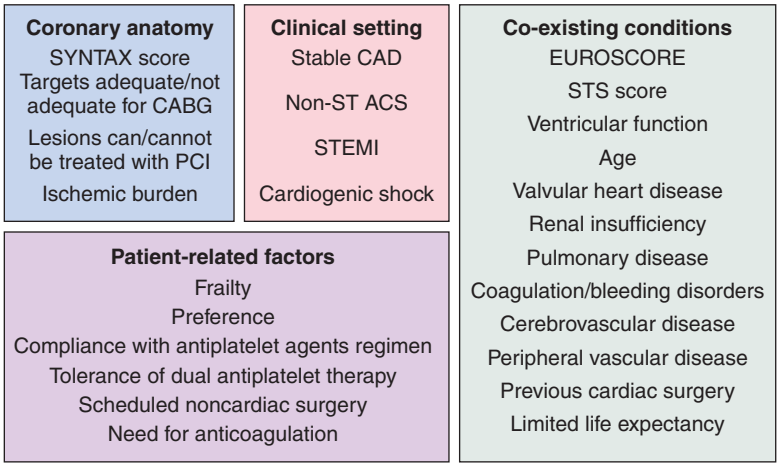


FIGURE 17-1 Parameters guiding the choice of revascularization strategy in diabetic patients. CABG = Coronary artery bypass grafting; STEMI = ST-segment elevation myocardial infarction; STS = Society of Thoracic Surgeons; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. *(Modified from Roffi M, Angiolillo DJ, Kappetein AP: Current concepts on coronary revascularization in diabetic patients,* Eur Heart J *32:2748-2757, 2011.)*

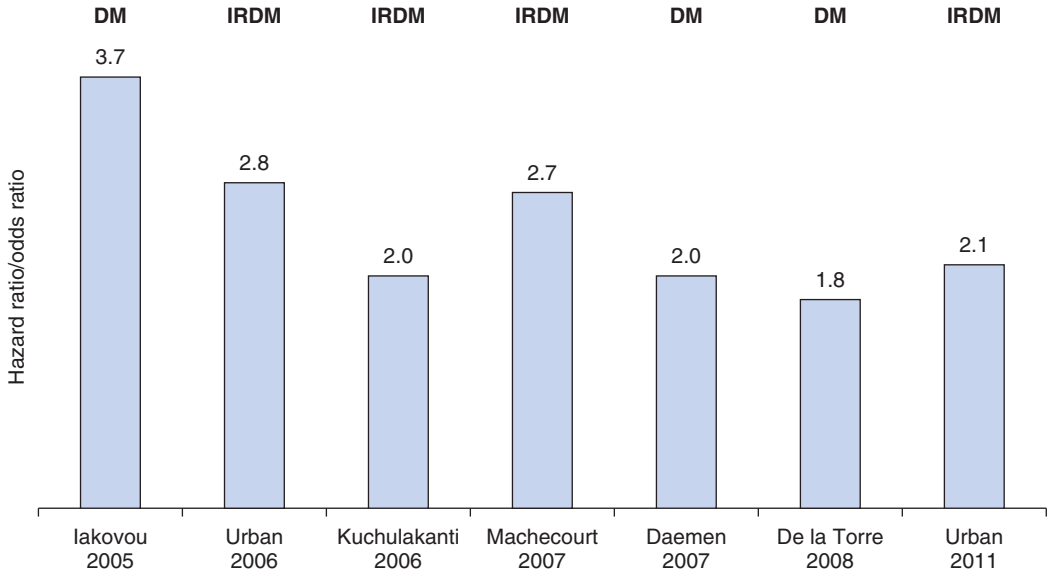


FIGURE 17-2 Studies have demonstrated the incremental independent risk associated with diabetes mellitus (DM) and insulin-requiring diabetes mellitus (IRDM) for stent thrombosis among patients treated with percutaneous coronary intervention using drug-eluting stents. Results are reported with the hazard ratio or odds ratio of multivariable analyses. *(Modified from Roffi M, Angiolillo DJ, Kappetein AP: Current concepts on coronary revascularization in diabetic patients,* Eur Heart J *32:2748-2757, 2011.)*

treatment effects on composite endpoints might be challenging to clinicians attempting to define the best strategy for clinical application.[30] Three questions have been suggested to help clinicians in decision making with their patients while interpreting results of clinical trials: (1) Are the components of the composite endpoint of similar importance to patients? (2) Did each component of the composite endpoint occur with similar frequencies? (3) Can one be confident that the component endpoints share similar relative risk reductions? If the answers to all these questions are "yes," clinicians might use with confidence the composite endpoints as the primary basis for decision making. If not, the individual component endpoints should be used as the basis for decision making.[31]

Similarly to the increased numbers of randomized controlled trials (RCTs) that have been performed over the past few decades, new meta-analysis designs have been developed, such as direct (head-to-head) RCT comparison and indirect RCT combination. Considering the methodologies described here, readers should be aware of potential controversies and biases among published studies of trials assessing the efficacy or safety of different revascularization options in subgroups of patients such as those with diabetes.

CONSERVATIVE STRATEGY

Few studies have compared conservative strategy versus revascularization procedures in patients with CAD. The Medicine, Angioplasty, or Surgery Study (MASS II) RCT compared in 611 patients—among them 190 patients with diabetes—three therapeutic options (medical management, angioplasty, and coronary artery bypass grafting [CABG]) with a follow-up of 5 years. Among diabetic patients, those treated with angioplasty or surgery had a lower mortality of 2 to 5 years compared with those who received medical treatment alone ($P = 0.039$).[32] The only trial focusing specifically on diabetic patients was the Bypass Angioplasty

Revascularization Investigation 2 Diabetes (BARI 2D) trial, which enrolled 2368 individuals with type 2 diabetes and stable CAD confirmed by angiography (stenosis ≥50% with positive stress test or ≥70% with classic symptoms). Patients with unstable symptoms, left main coronary disease, creatinine level of more than 2.0 mg/dL (177 μmol/L), a glycated hemoglobin level of more than 13.0%, class III or IV heart failure, or PCI or CABG within the previous 12 months were excluded. Patients were randomized to treatment with optimal medical therapy plus immediate revascularization versus optimal medical therapy alone, with the mode of revascularization (PCI or CABG) selected before randomization. The revascularization group included patients treated with PCI (n = 765) and with CABG (n = 347). This trial showed that intensive medical therapy alone was not significantly different from immediate revascularization plus intensive medical therapy in terms of MACEs (death, MI, and stroke) after 5 years of follow-up (77.2% for the revascularization group versus 75.9% for the medical group, $P = 0.70$). The corresponding survival rates were 88.3% and 87.8%, respectively.[17] A secondary analysis showed that patients selected to undergo CABG—that is, those with more advanced disease—derived a benefit from revascularization in terms of MACEs (22.5% CABG versus 30.4% medical therapy, $P = 0.01$). In those chosen to undergo PCI, medical treatment seemed to be an appropriate first-line strategy, particularly in those with less severe CAD. Of note, 23% of those initially allocated to medical therapy underwent revascularization within the 5 years.[33] The intervention strategy reduced the occurrence of symptoms and revascularization at 3 years—lower rates of worsening angina (8% versus 13%, $P < 0.001$), new angina (37% versus 51%, $P = 0.001$), and coronary revascularization (18% versus 33%, $P < 0.001$), and higher rate of angina-free status (66% versus 58%, $P = 0.003$). However, the results of BARI 2D may be difficult to reproduce in clinical practice because the patients were highly adherent to medical treatment, with the majority achieving all secondary prevention therapeutic goals. A secondary analysis of BARI 2D showed that, independent of the revascularization type, complete revascularization was associated with lower MACE rates.[12]

In conclusion, in low-risk diabetic patients (e.g., moderate CAD on coronary angiogram, stable symptoms, normal left ventricular and renal function) with excellent compliance with medical therapy, an initially conservative strategy is a valuable option. However, the results of the RCT cannot be extrapolated to higher-risk patients, to those with ACS, or to patients with unknown coronary anatomy. Independent of the revascularization strategy, optimal medical management, as described in **Chapters 12 to 16**, remains the cornerstone of treatment.

PERCUTANEOUS CORONARY INTERVENTION

General Considerations

Over the last years, improvements in techniques and design in coronary stenting have produced improved clinical results, and PCI became the major therapeutic option for coronary revascularization (**Tables 17-1** and **17-2**). After the introduction of balloon angioplasty by Grüntzig in 1977, coronary lesions were potentially treatable with balloon dilation leading to flow restoration.[34] The first human implantation of a stent was performed by Sigwart in Switzerland in 1987.[35] Compared with balloon angioplasty, BMSs resulted in a

TABLE 17-1 Summary of Percutaneous Coronary Intervention History

YEAR	IMPORTANT STEPS IN PERCUTANEOUS CORONARY INTERVENTION
1977	First percutaneous coronary angioplasty
1986	First BMS implantation
1993	Superiority of BMS versus balloon documented
1996	Adoption of dual antiplatelet therapy after BMS to prevent ST
2002	Superiority of DES versus BMS in term of restenosis documented
2002	Approval of SES in Europe
2003	Approval of SES by the FDA
2003	Superiority of PES versus BMS documented
2004	Approval of PES by the FDA
2005	Superiority of SES versus PES documented in patients with diabetes in terms of restenosis
2007	Superiority of SES versus BMS documented in patients with diabetes in terms of clinical outcomes
2008	Approval of ZES by the FDA
2008	Approval of EES by the FDA
2011	Noninferiority of EES versus SES documented in patients with diabetes
2012	Superiority of BES with biodegradable polymer versus BMS documented in patients with STEMI
2012	IPD suggesting improvement of safety and efficacy with biodegradable polymer DES versus durable polymer SES

BES = Biolimus-eluting stent; EES = everolimus-eluting stent; FDA = U.S. Food and Drug Administration; IPD, individual participant data; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; STEMI = ST-segment elevation MI; ZES = zotarolimus-eluting stent.

TABLE 17-2 Types of Coronary Stents

	COMPANY	SUBSTANCE	BIODEGRADABLE POLYMER
Bare metal stents	Multiple		
Bioactive stents			
TITAN	HexaCath		
First-generation drug eluting stents			
CYPHER	Cordis	Sirolimus	
TAXUS	Boston Scientific	Paclitaxel	
Newer-generation drug eluting stents			
PROMUS	Boston Scientific	Everolimus	
ENDEAVOR	Medtronic	Zotarolimus	
XIENCE	Abbot Vascular	Everolimus	
RESOLUTE	Medtronic	Zotarolimus	
BIOMATRIX	Biosensors	Biolimus	X
ORSIRO	Biotronik	Sirolimus	X
NOBORI	Terumo	Biolimus	X
Bioabsorbable scaffolding			
ABSORB	Abbot Vascular	Everolimus	X

lower angiographic restenosis rate and better event-free survival.[36–38] However, some concerns regarding clinically relevant in-stent restenosis with BMSs arose because of the phenomenon of neointimal process.[39,40] Consequently, DES devices were developed with coated antiproliferative agents that inhibit hyperplasia, especially of the smooth muscle cells, and reduce in-stent restenosis and the need for TLR.[41] This benefit of sirolimus-eluting stents (SES) was also observed in the subgroup of patients with diabetes in the SIRIUS trial, although the effect size was less evident in those with diabetes requiring insulin treatment.[42] The superiority of DESs in terms of in-stent restenosis was also observed with paclitaxel-eluting stents (PESs) in the TAXUS trials.[43] DESs have dramatically changed the approach to CAD treatment, especially in patients with multivessel disease, reducing the need for surgical procedures.[40,44] The risk of ST and its dramatic consequences, such as MI or death, has been a long source of debate and concerns related to the use of DESs.[45–47] The occurrence of ST was attributed to a delayed endothelialization of the permanent metallic struts.[27,45] However, pooled data analyses from RCT did not show a significant increased risk of ST with the use of DESs compared with BMSs, even in patients with diabetes and those with ACS.[48–50] An increased risk of death and MI was observed with clopidogrel discontinuation after DES implantation,[51] also in patients with diabetes, independent of the implanted stent (BMS or DES).[52,53] Although the risk of ST is currently low, it is a major issue, especially among patients with diabetes, and prompted investigation for effective antithrombotic and antiplatelet therapies (see the discussion of adjunctive pharmacologic treatment later in this chapter), as well as more effective coronary stent devices, such as new-generation DESs using bioabsorbable polymers (e.g., ABSORB, Abbot Vascular, Santa Clara, California, United States).

Bare-Metal Stents versus Drug-Eluting Stents

Several registries, RCTs, and pooled meta-analyses have compared BMSs with DESs in patients with diabetes in terms of efficacy (reduced revascularization) and safety (death, MI, and ST) (**Table 17-3**). The use of DESs compared with

TABLE 17-3 Studies Comparing Drug-Eluting Stents with Bare-Metal Stents in Patients with Diabetes

TRIAL	YEAR	NUMBER	FOLLOW-UP	MORTALITY	TLR	MACES	DEFINITE OR PROBABLE ST
RCTs Comparing BMSs with DESs in Patients with Diabetes							
SESs Versus BMSs							
DIABETES[55]	2007	160	24 months	2.6% versus 3.8%	7.7% versus 35.0%*	12.8% versus 41.3%*	3.8% versus 1.3%
DESSERT[56]	2008	150	12 months	4.4% versus 2.9%	5.9% versus 30.0%*	22.1% versus 40.0%*	1.5% versus 1.4%
SCORPIUS[57]	2007	200	12 months	5.0% versus 4.0%	5.3% versus 21.1%*	14.7% versus 35.8%*	2.1% versus 2.2%
DECODE[58]	2008	83	12 months	0 versus 6.9%	13.0% versus 34.5%*	24.8% versus 41.4%*	0% versus 0%
SIRIUS[42]	2004	279	9 months	NA	6.9% versus 22.3%*	9.2% versus 25.0%*	0.7% versus 0.8%
RAVEL[59]	2004	44	12 months	5.3% versus 4.0%	0% versus 32%*	10.5% versus 48.0%*	0% versus 0%
SES-SMART[60]	2005	74	8 months	0% versus 2%	17.0% versus 31%	24.0% versus 38.0%	3.0% versus 4.0%
PESs Versus BMSs							
HORIZONS-AMI[61]	2011	478	12 months	6.1% versus 7.2%*	5.2% versus 11.2%*	13.5% versus 21%	3.1% versus 4.5%
TAXUS-IV[62]	2005	318	12 months	1.9% versus 2.5%*	7.4% versus 20.9%*	15.6% versus 27.7%*	NA
Cohort Studies Comparing DESs Versus BMSs in Patients with Diabetes							
SESs versus BMSs							
RESEARCH and T-SEARCH[63]	2007	458	24 months	13.3% versus 9.8%	15.3% versus 19.5%	28.9% versus 29.7%	4.4% versus 0.8%
PESs versus BMSs							
RESEARCH and T-SEARCH[63]	2007	502	24 months	11.5% versus 9.8%	9.7% versus 19.5%*	21.2% versus 29.7%	2.0% versus 0.8%
DESs versus BMSs							
Minha et al[64]	2011	1806	48 months	13.0% versus 17.1%*	10.0% versus 15.5%*	28.6% versus 35.0%*	NA
Pooled Data Analyses Comparing DESs Versus BMSs in Patients with Diabetes							
				MORTALITY	**TLR**	**MI**	**DEFINITE OR PROBABLE ST**
SESs versus BMSs							
Spaulding et al[48]	2007	428	48 months	4.4% versus 12.2%*	NA	6.5% versus 8.2%	6.6% versus 3.9%
Stettler et al[53]	2008	3852	NA	HR 0.88 (95% CI 0.55-1.30)	HR 0.29 (95% CI 0.19-0.45)*	HR 0.68 (95% CI 0.43-1.12)	HR 0.72 (95% CI 0.04-10.8)
Bangalore et al[54]	2012	22,855 patient-years		HR 1.00 (95% CI 0.73-1.39)	HR 0.34 (95% CI 0.25-0.44)*	HR 0.71 (95% CI 0.49-1.05)	HR 0.64 (95% CI 0.36-1.14)
PESs versus BMSs							
Kirtane et al[65]	2008	827	48 months	8.4% versus 10.3%	12.4% versus 24.7%*	6.9% Versus. 8.9%	1.4% versus 1.2%

TABLE 17-3 Studies Comparing Drug-Eluting Stents with Bare-Metal Stents in Patients with Diabetes—cont'd

				MORTALITY	TLR	MI	DEFINITE OR PROBABLE ST
Stettler et al[53]	2008	3852	NA	HR 0.91 (95% CI 0.60-1.38)	HR 0.91 (95% CI 0.26-0.56)*	HR 0.85 (95% CI 0.54-1.43)	HR 3.54 (95% CI 0.23-78.6)
Bangalore et al[54]	2012	22,855 patient-years		HR 0.96 (95% CI 0.70-1.38)	HR 0.46 (95% CI 0.34-0.63)*	HR 0.82 (95% CI 0.55-1.22)	HR 0.78 (95% CI 0.45-1.54)
DESs versus BMSs							
Kumbhani et al[66]	2008	2951	12 months	HR 0.64 (95% CI 0.32-12.8)	HR 0.35 (95% CI 0.27-0.46)*	HR 0.57 (95% CI 0.32-0.99)*	HR 0.41 (95% CI 0.13-1.27)

CI = Confidence interval; HR = hazard ratio; NA = not applicable.
*P < 0.05.

BMSs dramatically reduces the risk of repeat revascularization and has no evident harmful effect—and may indeed be even beneficial—in terms of MI or ST reduction. The most consequent analysis was performed with use of data from 22,844 patients with diabetes from 42 RCTs and reported a significant reduction in TVR (37% versus 69%) with DESs compared with BMSs.[54] **Figure 17-3** shows the cumulative probability of ST in patients with diabetes treated with DES or BMS based on results from a meta-analysis of 11 RCTs.[50] The difference of very late ST (>1 year) was not significant between DESs and BMSs. Accordingly, current European guidelines on myocardial revascularization recommend DES as the device of choice for diabetic patients undergoing PCI (Class I, Level of Recommendation A).[21] On the other hand, recent U.S. guidelines on the management of stable CAD do not mention a specific recommendation regarding the subtype of PCI device for revascularization of diabetic patients.[67]

Drug-Eluting Stents

DESs have to be considered as the first-line treatment for diabetic and nondiabetic patients undergoing PCI. **Table 17-4** summarizes RCT and meta-analyses that assessed clinical outcomes in patients with diabetes treated with DES (i.e., the SES [CYPHER; Cordis, Miami Lakes, Florida] and the PES [TAXUS; Boston Scientific, Natick, Massachusetts]). All DESs have been reported to be safe and efficacious in patients with diabetes, especially in the reduction of TVR, and no evidence is available to recommend preferential use of one of the available DES devices in such patients.[68] Some concerns persisted regarding the very late ST risk associated with DESs. Whether ST rates vary among different DESs remains controversial, because no RCT has been adequately powered to draw conclusions and the magnitude of these trials differed [27]; therefore the new-generation DESs with new drugs and/or biodegradable polymers have been developed. Overall, newer-generation DESs (everolimus-eluting stent [EES; Xience V, Abbot Vascular, Santa Clara, California; PROMUS, Boston Scientific]) appear to convey superior results compared with the first-generation DESs and are effective in the prevention of restenosis.[44,69,70] However, some debate still persists with regard to patients with diabetes who require insulin treatment, because the clinical advantage of EES is not pronounced in this population.[71]

The new design of secondary DESs with bioabsorbable polymers allows the restoration of the vessel's biologic properties[72] and might be particularly advantageous in patients with diabetes because of the underlying increased risk of thrombotic events.[73,74] The available data in the overall population showed noninferiority or even an advantage of biodegradable stents (biolimus-eluting stents) compared with SESs in term of TVR, MI, and ST reduction.[75–77] However, more data are needed to define the potential long-term benefit of biodegradable DESs in patients with diabetes.

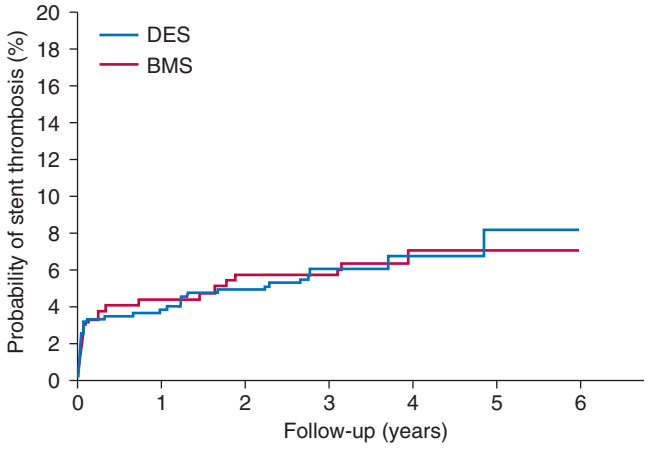


FIGURE 17-3 Kaplan-Meier curves of probability of ST according to the stents groups in patients with diabetes. *(Modified from De Luca G, Dirksen MT, Spaulding C, et al: Meta-analysis comparing efficacy and safety of first generation drug-eluting stents to bare-metal stents in patients with diabetes mellitus undergoing primary percutaneous coronary intervention,* Am J Cardiol *111:1295-1304, 2013.)*

Percutaneous Coronary Intervention versus Bypass Surgery

The optimal revascularization modality in patients with multivessel CAD has been a source of debate for decades in patients with diabetes, and this debate is expected to continue with the new era of DES stents and antithrombotic and antiplatelet therapies.[78] In this section, we consider studies that have addressed the issue of revascularization in diabetic patients with multivessel CAD (PCI versus CABG). **Tables 17-5** and **17-6** summarize the results from RCTs, meta-analyses, and registries. We discuss in detail two major studies in the field.

The SYNTAX RCT compared PCI (PES) versus CABG in patients with diabetes and a total study population of 1800 patients with left main and/or multivessel CAD. The results were statistically not different in terms of the primary composite endpoint at 1 year (death, stroke, MI) between both revascularization methods in nondiabetic patients (6.8% CABG versus 6.8% PES, $P = 0.97$) and diabetic patients (10.3% CABG versus 10.1% PES, $P = 0.96$).[79] However, in subgroup analyses, mortality was higher after PES in patients

TABLE 17-4 Studies Comparing Different Drug-Eluting Stents in Patients with Diabetes

TRIAL	YEAR	NUMBER	MAXIMUM FOLLOW-UP	MORTALITY	TLR	MACES	ST
RCTs Comparing Different DESs in Patients with Diabetes							
SESs versus PESs							
ISAR-DIABETES	2005	250	9 months	3.2% versus 4.8%	6.4% versus 12.0%	NA	NA
DES-DIABETES[92]	2008	400	9 months	0% versus 0.5%	2.0* versus 7.5%*	2.0% versus 8.0%*	0.5% versus 0%
DES-DIABETES[93]	2010	400	48 months	3.0% versus 5.0%	7.5% versus 12.0%	11.0% versus 16%	4% versus 1.5%
DiabeDES[94]	2009	153	8 months	2.6% versus 1.3%	6.5% versus 11.8%	7.9% versus 14.5%	0% versus 2.6%
Hong et al[95]	2010	169	36 months	3.5% versus 2.4%	2.4% versus 7.1%	5.9% versus 9.5%	1.2% versus 3.6%
Kim et al[96]	2008	169	6 months	1.2% versus 1.2%	2.4% versus 4.8%	NA	NA
Naples-DIABETES[97]	2011	151	36 months	6.6% versus 4.0%	2.6% versus 9.3%	13.2% versus 17.5%	1.3% versus 0%
SIRTAX[18]	2008	201	24 months	8.3% versus 10.8%	7.4% versus 17.2%*	14.8% versus 25.8%*	0.9% versus 3.2%
ZESs versus PESs							
ENDEAVOR IV[98]	2009	477	12 months	0.0% versus 0.9%	6.9% versus 5.8%	6.9% versus 7.2	0.9% versus 0.4%
Naples-DIABETES[97]	2011	150	36 months	5.3% versus 4.0%	18.7% versus 9.3%	35.6% versus 17.5%*	4.0% versus 0%
ZESs versus SESs							
Naples-DIABETES[97]	2011	151	36 months	5.3% versus 6.6%	18.7% versus 2.6%	35.6% versus 13.2%*	4.0% versus 1.3%
SORT-OUT III[99]	2011	337	18 months	8.3% versus 5.4%	12.4% versus 1.2%*	18.3% versus 4.8%*	1.8% versus 0.0%
EESs versus SESs							
ESSENCE-DIABETES[100]	2011	300	12 months	1.3% versus 3.3%†	0.7% versus 2.6%†	2.0% versus 5.3%†	0.7% versus 0.7%†
EESs versus PESs							
SPIRIT IV[101]	2010	1185	12 months	1.6% versus 0.8%†	4.2% versus 4.7%	6.4% versus 7.1%	0.8% versus 1.3*
Pooled Data Analyses Comparing Different DES in Patients with Diabetes							
SESs versus PESs							
Mahmud et al[102]	2008	2422	12 months	NA	7.6% versus 8.6%	12.9% versus 15.4%	0.6% versus 1.5%*
Stettler et al[103]	2006	5455 person-years		NA	RIRR 0.86 (0.40-1.86)	RIRR 0.86 (0.21-1.71)	NA
Mahmud et al[102]	2008	10156	12 months	NA	10.5% versus 10.5%	15.9% versus 16.9%	NA
Kufner et al[104]	2011	1183	48 months	HR 1.04 (95% CI 0.74-1.45)	HR 0.66 (95% CI 0.47-0.91)	NA	HR 1.00 (95% CI 0.31-3.30)
				Mortality	***TLR***	***MI***	***ST***
Stettler at al[53]	2008	3852	NA	HR 0.95 (95% CI 0.63-1.43)	NA	HR 0.80 (95% CI 0.55-1.27)	HR 0.20 (95% CI 0.02-1.04)
PESs versus SESs							
Bangalore et al[54]	2012	22,855 patient-years		HR 0.97 (95% CI 0.71-1.32)	HR 1.36 (95% CI 1.05 versus 1.82)*	HR 1.16 (95% CI 0.80-1.64)	HR 1.23 (95% CI 0.74-2.17)
EESs versus SESs							
Bangalore et al[54]	2012	22,855 patient-years		HR 0.83 (95% CI 0.45-1.41)	HR 0.81 (95% CI 0.46-1.27)	HR 0.74 (95% CI 0.32-1.46)	HR 0.85 (95% CI 0.36-2.02)
EESs versus PESs							
Stone et al[105]	2011	1869	24 months	3.9% versus 2.9%	5.5% versus 6.1%	4.2% versus 4.9%	1.6% versus 2.0%
Bangalore et al[54]	2012	22,855 patients years		HR 0.86 (95% CI 0.47-1.45)	HR 0.60 (95% CI 0.33-0.93)	HR 0.64 (95% CI 0.28-1.19)	HR 0.69 (95% CI 0.29-1.55)

EES = Everolimus-eluting stent; RIRR = ratio incidence rate ratio; ZES = zotarolimus-eluting stent. *$P < 0.05$ for superiority trial.
†$P > 0.05$ for noninferiority trial.

with diabetes and highly complex lesions (13.5% PCI versus 4.1% CABG, $P = 0.04$), and PES resulted in higher TVR in patients with diabetes (20.3% versus 6.4% CABG, $P > 0.001$). The SYNTAX follow-up at 3 years showed that patients with diabetes treated initially with PCI-PES experienced a higher risk of MACEs (37.0% PES versus 22.9% CABG, $P = 0.002$) or repeat revascularization (28.0% PES versus 12.9% CABG, $P < 0.001$) compared with the CABG-treated group.[80] After exclusion of the clinically less impactful TVR component endpoint, the composite endpoint of death, stroke, and MI was not statistically different between the groups (16.3% for PCI versus 14.0% for CABG, $P = 0.53$). The authors concluded that PCI might be preferred for patients with less complex left main and/or three-vessel

TABLE 17-5 Pooled Analysis of Studies Comparing Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft Surgery in Population of Patients with Diabetes and Multivessel Coronary Artery Disease

STUDY DESIGN	YEAR	DIABETIC POPULATION	FOLLOW-UP (YEARS)	EFFECT OF TREATMENT ON OUTCOMES
IPD from 4 RCTs[106]	2008	275 with PCI (BMS) and 268 with CABG	5	Similar mortality (7.9% versus 12.4%, $P=0.09$) and MACEs (21.4% versus 20.9%, $P=0.9$), but increased revascularization with PCI (29.7% versus 9.2%, $P<0.001$)
IPD from 10 RCTs[17]	2009	618 with PCI (BMS or balloon) and 615 with CABG	Median 5.9	Reduction of mortality with CABG (HR 0.70, 95% CI 0.56-0.87)
IPD from 3 registries[107]	2012	846 with PCI (DES or BMS) and 915 with CABG	Median 5.5	Reduction of mortality (HR 0.70, 95% CI 0.55-0.88) and MACEs (HR 0.71, 95% CI 0.57-0.89), but increased revascularization with PCI (HR 4.55, 95% CI 3.27-6.32)

IPD = Individual participant data; MACE = major averse cardiovascular event (death, MI, or stroke).

TABLE 17-6 Recent Randomized Controlled Trials Comparing Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft Surgery in Population of Patients with Diabetes and Multivessel Coronary Artery Disease

STUDIES	YEAR	DIABETIC POPULATION	FOLLOW-UP (YEARS)	EFFECT OF TREATMENT ON OUTCOMES
SYNTAX[79]	2009	452 patients (221 treated with CABG and treated 231 with PES)	1	All-cause death, CVA, MI: 10.3% CABG versus 10.1% PES ($P=0.96$) Revascularization rate: 6.4% CABG versus 20.3% PCI ($P<0.001$)
CARDIA[108]	2010	510 patients (254 treated with CABG and 256 treated with PCI including both BMS and DES)	1	Composite rate of death, MI, CVA: 10.5% CABG versus 13.0% PCI (HR 1.25, 95% CI 0.75-2.09, $P=0.39$) Rates of death, MI, CVA, or repeat revascularization: 11.3% CABG versus 19.3% PCI (HR 1.77, 95% CI 1.11-2.82)
ARTS I and II[109]	2011	367 patients (159 SES, 96 CABG, 112 BMS)	5	Rate of MACE and CVA was significantly higher with BMS (BMS 53.6% versus CABG 23.4% versus SES 40.5%, $P<0.01$), but not mortality (BMS 13.6% versus CABG 8.6% versus SES 9.0%, $P>0.05$)
SYNTAX[80]	2011	452 patients (221 treated with CABG and 231 treated with PES)	3	All-cause death, CVA, MI, and TVR: 22.9% CABG versus 37.0% PES ($P=0.002$) Revascularization rate: 12.9% CABG versus 28.0% for PES ($P<0.001$)
FREEDOM[83]	2012	1900 patients (947 treated with CABG and 953 treated with DES)	5	Death from any cause, nonfatal MI, or nonfatal CVA: 18.7% for CABG versus 26.6% for PCI ($P=0.005$)
VA CARDS[110]	2013	198 (97 treated with CABG and 101 treated with DES)	2	All-cause mortality: 5.0% for CABG versus 21.0% for PCI (HR 0.30, 95% CI 0.11-0.80) Nonfatal MI: 15.0% for CABG versus 6.2% for PCI (HR 3.32, 95% CI 1.07-10.30)

CVA = Cerebrovascular accident.

lesions (SYNTAX scores ≤22), but CABG should be the option of choice for patients with more complex left main coronary artery disease or three-vessel anatomic disease, especially for patients with diabetes.[81] Recently, the 5-year follow-up from the overall population has been published, and results confirmed that CABG should be the choice for patients with complex lesions (intermediate and high SYNTAX scores) and that PCI is an acceptable treatment for less complex lesions (low SYNTAX scores).[82]

The FREEDOM RCT compared PCI (DES) with CABG in 1900 diabetic patients with multivessel CAD and showed an increased risk of the primary outcome of MACEs in the PCI group compared with the CABG group after 5 years of follow-up (26.6% versus 18.7%, $P=0.005$).[83] CABG was superior to PCI in terms of a reduced overall death rate (16.3% versus 10.9%, $P=0.049$) and MI (13.9% versus 6.0%, $P<0.001$) but inferior to PCI in terms of a higher rate of stroke at 5 years (2.4% in the PCI group and 5.2% in the CABG group, $P=0.03$). However, debate persists, because the PCI option yielded comparable results to CABG during the first 2 years of follow-up, with event curves thereafter diverging ultimately to reveal an absolute 5-year survival benefit of 5.4% for CABG (95% CI 1.5-9.2). **Figure 17-4** summarizes the findings of the 5-year follow-up of the SYNTAX and FREEDOM trials in patients with diabetes according to the baseline anatomic complexity. Both studies reported a benefit of treatment with CABG in patients with complex disease (SYNTAX score ≥33 points) in terms of composite endpoint reduction (death, stroke, MI). In patients with less complex disease (SYNTAX score <22 points), PCI and CABG results did not differ significantly, suggesting that PCI is an acceptable alternative. In patients with intermediate disease (SYNTAX score 23 to 32 points), the FREEDOM trial reported a benefit of CABG not confirmed in the SYNTAX trial, suggesting that a consensus for the optimum treatment should be discussed by the "heart team," including both cardiac surgeons and interventional cardiologists.

In current practice, patients with diabetes and multivessel CAD should be informed about the potential survival benefit with CABG,[32] and the treatment chosen should ultimately be based on the patient's concerns and preferences after a discussion within a multidisciplinary heart team composed of a cardiac surgeon and an interventional cardiologist.[67,82] This shared-decision discussion at this stage is aimed at offering

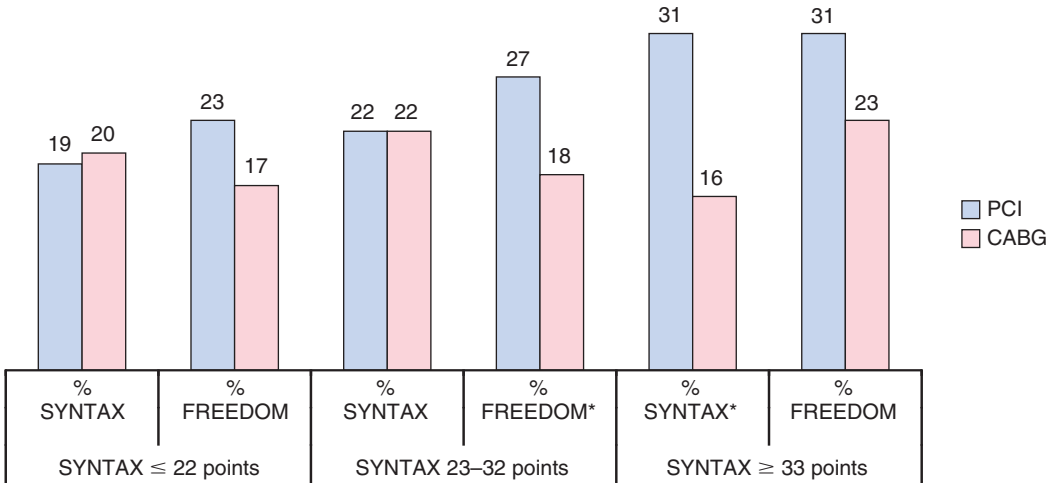


FIGURE 17-4 Five-year outcomes of patients with diabetes according to the anatomic lesion complexity (SYNTAX score) and revascularization treatment (PCI versus CABG). Binary event rates of the composite endpoint of death, stroke, and MI in the SYNTAX[111] and FREEDOM trials.[83] *$P < 0.05$.

to patients the most appropriate and evidence-based treatment recommendations with all the transparency of the available current evidence. Overall, the revascularization strategy should be based on and guided by anatomic and clinical characteristics, as well as interventional SYNTAX score (http://syntaxscore.com) and surgical EUROSCORE (www.euroscore.org) reflecting the complexity and its influence on anticipated results from each revascularization modality and its risks. Recently the SYNTAX II score has been developed and estimates the 4-year mortality for each treatment (PCI versus CABG). The score contains eight variables: anatomic SYNTAX score, age, creatinine clearance, left ventricular ejection fraction, presence of unprotected left main CAD, peripheral artery disease, female gender, and chronic obstructive pulmonary disease. However, the presence of diabetes was not important for decision making between CABG or PCI.[84] Although the impact of newer-generation DESs needs to be evaluated, the threshold for CABG should be definitively lower in diabetic patients than in their nondiabetic counterparts.

ADJUNCTIVE PHARMACOLOGIC TREATMENT

The role of antiplatelet treatment in patients with diabetes and chronic stable CAD or ACS is described in **Chapters 16** and **21**; the most relevant findings related to elective PCI are summarized here. In patients with diabetes and CAD, a longer duration of clopidogrel therapy (>9 months) after BMS or DES implantation was associated with a lower incidence of death or MI compared with patients who discontinued taking the drug within 6 months and within 6 to 9 months.[52] Among clopidogrel nonusers, the occurrence of death-MI or death did not significantly differ by the stent type. In a large cohort after DES implantation, the continuation of clopidogrel (for at least 24 months) was associated with a reduction in risk for death and death or MI compared with patients who discontinued clopidogrel at 6 or 12 months. However, the authors concluded that an RCT was required to definitely confirm the optimal duration of clopidogrel.[85] Dual antiplatelet therapies are recommended as adjuncts to PCI, especially a loading dose of acetylsalicylic acid (ASA) or clopidogrel (600 mg) at least 2 hours and preferably 6 hours before the procedure. The long-term continuation daily dose should be 75 to 150 mg ASA and 75 mg clopidogrel; a higher maintenance dose (150 mg) has been proposed in patients with a high thrombotic risk (e.g., those with diabetes).[21] Diabetic patients more frequently have a suboptimal platelet response to clopidogrel compared with nondiabetic patients. For that reason, more potent P2Y12 inhibitors (prasugrel and ticagrelor) may be of particular benefit in the diabetic patients. The Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) trial was a prospective, randomized, double-blind, crossover study designed to perform serial measures of platelet inhibition in diabetic patients treated with (1) prasugrel (60-mg loading dose and 10-mg maintenance dose) compared with (2) clopidogrel (600-mg loading dose and 150-mg maintenance dose). Prasugrel was associated with a greater degree of platelet inhibition (89.3% versus 27.7%, $P < 0.0001$), both with loading and maintenance periods, compared with clopidogrel.[86] The benefit of prasugrel was confirmed in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) in patients with ACS, with a significant reduction in clinically relevant MACEs compared with the use of clopidogrel.[87] Ticagrelor was assessed in the Study of Platelet Inhibition and Patient Outcomes (PLATO) in patients with ACS in comparison with clopidogrel. Despite the larger diabetic population enrolled in PLATO compared with TRITON-TIMI 38, the benefit observed in diabetic patients with ticagrelor did not reach statistical significance.[88] Whereas newer P2Y12 inhibitors (prasugrel and ticagrelor) are superior to clopidogrel in patients with diabetes and ACS, no comparative data in the setting of stable or elective PCI are available, and more data are needed to recommend specific adjunctive pharmacologic therapy for diabetic patients undergoing PCI.

With respect to anticoagulants, bivalirudin was reported to be safe and effective in reducing cardiac mortality at 30 days and 1 year in 593 patients with diabetes and ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI compared with unfractionated heparin plus glycoprotein IIb//IIIa (GPIIb/IIIa) receptor inhibitors in a subgroup analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.[89] The GPIIb-IIIa inhibitors should be used in complex situations (thrombus, slow flow, vessel

closure, very complex elective procedures) in elective procedures, and has shown a reduction in mortality when used in patients with diabetes in the context of ACS.[90] The current role of these agents in the setting of potent P2Y12 inhibitors and newer anticoagulants needs to be defined.

Finally, an RCT comparing dual antiplatelet therapy with triple antiplatelet therapy (i.e., aspirin, clopidogrel, and cilostazol) in 400 patients with diabetes treated with a DES showed a decrease in 6-month stent restenosis (8.0% versus 15.6%, $P=0.033$) and 9-month TLR (2.5% versus 7.0%, $P=0.034$).[91] Although cilostazol is not commercially available in most European states, it is available in the United States, although not approved for this indication. Those findings need to be replicated in a larger population.

FUTURE STRATEGIES TO IMPROVE PERCUTANEOUS CORONARY INTERVENTION RESULTS

In terms of medical devices, the initial encouraging data from use of bioabsorbable scaffolds suggest that this device may further improve PCI-related outcomes, such as ST and target vessel MI. However, no compromise in terms of efficacy (i.e., restenosis and TVR) will be acceptable, particularly in the diabetic population. Therefore, large-scale RCTs against newer conventional DESs are needed before this technology may be broadly applied. The development of newer P2Y12 inhibitors definitively improved the outcomes of patients with diabetes and ACS undergoing PCI. Further studies are needed to investigate whether a benefit may be present also for patients with diabetes and stable CAD. In addition, drugs involving new promising molecules that inhibit platelet function are in development, such as ramatroban and terutroban (thromboxane receptor inhibitors) and picotamide and ridogrel (combined thromboxane synthase inhibitors and receptor blockers), and might potentially open new therapeutic possibilities for diabetic patients with CAD.

With respect to revascularization strategy, the mechanisms of the apparent survival benefit in diabetic patients with advances CAD still need to be understood. In the future this may allow selection of the best revascularization strategy for the individual diabetic patient. Aggressive secondary prevention based on strict control of associated cardiovascular risk factors and on the still-to-be-defined optimal target of glucose metabolism control remains the cornerstone of the treatment of diabetic patients with CAD, independent of the revascularization strategy.

SUMMARY

Diabetic patients constitute a subgroup of patients at increased risk of unfavorable outcomes following PCI because of more severe and extensive CAD, as well as higher rates of restenosis and ST. Improvements in techniques and design in coronary stenting have resulted in improved clinical results, and PCI has become the major therapeutic option for coronary revascularization in patients with diabetes. DESs have dramatically changed the approach to CAD treatment, especially in patients with multivessel disease, reducing stent restenosis and the need for surgical procedures. In low-risk diabetic patients with excellent compliance with medical therapy, an initial conservative strategy is a valuable option. In patients with diabetes and multivessel CAD, PCI might be preferred for patients with less complex lesions, but CABG should be the option of choice for patients with more complex left main coronary disease or three-vessel anatomic disease.

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18 Role of Coronary Artery Bypass Surgery in Diabetes and Perioperative Glucose Management



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Diabetes mellitus is a major contributor to the development of cardiovascular illness and results in a twofold to fourfold increase in coronary artery disease (see also **Chapter 7**).[1] It accounts for approximately one fourth of all patients who undergo coronary revascularization procedures each year and is more likely to be associated with diffuse and extensive three-vessel and left main disease.[2,3] This contributes to increased morbidity and mortality after coronary artery bypass graft (CABG) surgery and the need for revascularization procedures.[4–6]

This chapter reviews the short- and long-term outcomes of CABG surgery in patients with diabetes mellitus and compares them with the results achieved with percutaneous coronary intervention (PCI) to determine the optimal strategy for coronary revascularization in these high-risk patients (see also **Chapter 17**). The detrimental effects of hyperglycemia in the CABG patient with diabetes are discussed, and data are presented to show that through achievement of glycemic control in these patients, perioperative morbidity and mortality can be reduced, long-term survival improved, and the incidence of recurrent ischemic events decreased.

CORONARY ARTERY BYPASS GRAFT SURGERY IN PATIENTS WITH DIABETES

Risk Profiles and Comorbidities

Patients with diabetes undergoing CABG surgery have an increased incidence of associated comorbidities, including chronic renal failure, peripheral vascular disease, reduced ejection fraction (EF), congestive heart failure (CHF), cardiomyopathy, hypertension, and previous myocardial infarctions (MIs), compared with nondiabetic patients.[7–10] It is therefore imperative that a thorough preoperative evaluation be performed before CABG surgery in these patients in an attempt to minimize postoperative morbidity and mortality.

In the presence of stable symptoms, surgery should be delayed for 3 to 5 days following cardiac catheterization to avoid renal dysfunction caused by contrast nephropathy.[11] Preoperative assessment with carotid ultrasound and ankle brachial indices helps to detect critical peripheral vascular lesions that may lead to strokes and lower-extremity ischemia and assists in determining whether patients are candidates for intra-aortic balloon pump (IABP) placement. Transthoracic echocardiography helps to detect global and regional wall motion abnormalities and underlying valvular disease that may need to be addressed at the time of surgery. In patients with a smoking history, pulmonary function studies are helpful to determine the need for preoperative bronchodilators and to optimize pulmonary toilet to avoid prolonged postoperative ventilation. However, despite adjustments for related comorbidities, diabetes is still a major independent risk factor for increased early and late mortality after CABG surgery.[12]

Early Outcomes

Compared with nondiabetic patients, patients with diabetes who undergo CABG surgery have a higher perioperative mortality (3.2% to 3.7% versus 2.2% to 2.5%) and increased morbidity.[13] They also have an increased incidence of sternal wound infections and mediastinitis,[5] renal dysfunction necessitating replacement therapy,[14] strokes,[15] low cardiac output, and need for inotropic and IABP support,[16,17] all of which result in prolonged intensive care unit (ICU) and hospital stays.



Late Outcomes

Patients with diabetes also have poor long-term (5- to 10-year) survival compared with nondiabetic patients.[18] This is especially true for diabetic patients who require insulin treatment.[19,20] In fact, some studies suggest that in contrast to diabetic patients receiving only oral agents, only diabetic patients requiring insulin have significantly worse long-term survival compared with nondiabetic patients.[5,8,21–24] Certain groups of diabetic patients appear to have worse long-term survival. Leavitt and coworkers found that patients with diabetes and concomitant peripheral vascular disease and renal failure had significantly worse 10-year survival compared with nondiabetic patients and with diabetic patients without these comorbidities.[25]

Long-term outcomes for diabetic patients with reduced left ventricular (LV) function (EF below 40%) has varied. Trachiotis and coworkers in their review of 11,830 CABG patients found that in patients with an EF below 35%, diabetic patients had a 59% increase in the risk of long-term mortality ($P<0.0001$).[26] Whang and coworkers found that in diabetic patients with an EF below 36% there was a 44% higher risk for rehospitalization for any cause ($P=0.0001$) and a 24% higher risk of readmission for cardiac issues ($P<0.05$) over a 6-year period.[27] Others have found no difference in long-term mortality in diabetic patients with reduced EF.[28,29] This difference in outcomes may be a result of differences in myocardial viability in the patients who were studied. Patients with diabetic cardiomyopathy and reduced EF from longstanding hypertension and poor glycemic control may ultimately develop hypertrophy and fibrosis that leads to diastolic and systolic dysfunction.[30] Diabetic patients with reduced but viable myocardium may derive a much larger benefit from CABG surgery than patients with cardiomyopathies with fibrotic and nonviable muscle.

Graft Patency

As noted in the preceding sections, patients with diabetes have less freedom from recurrent angina and the need for recurrent revascularization procedures. A major determinant for recurrent ischemic events after CABG surgery is graft patency. Diabetes was shown in earlier studies such as the Coronary Artery Surgery Study (CASS) to be an independent predictor of decreased graft patency.[31,32] In 2008, Singh and coworkers reported the impact of diabetes on graft patency after CABG surgery in 440 patients (115 with diabetes) followed for 1 year.[33] Multivariable regression analyses found that diabetes was an independent predictor of 1-year graft occlusion (14.4% versus 9.7%; $P=0.03$). The large majority of these conduits were saphenous veins. Radial artery grafts have also been found to have more spasm and a higher incidence of short-term occlusion in diabetic patients.[34]

The internal mammary artery (IMA) has the highest graft patency of any CABG conduit and is especially important for diabetic patients. Hirotani and coworkers found that diabetic patients who had at least one patent IMA graft had significantly better overall survival and improved cardiac event–free survival compared with saphenous vein grafts alone.[35] In an attempt to improve overall graft patency in diabetic CABG patients, it has been suggested that bilateral IMAs be routinely used for revascularization. Concerns have been raised regarding the possibility of higher rates of sternal dehiscence and mediastinal infections when bilateral IMAs are used in diabetic patients. In an attempt to define the benefits and risks of bilateral IMAs, Endo and coworkers studied outcomes of bilateral versus unilateral IMA revascularization in patients with diabetes.[36] The cohort consisted of 1131 patients, 467 (41.3%) of whom had type 2 diabetes. In this group, 277 received a single IMA and 190 patients had bilateral IMAs. The hospital mortality and rate of deep sternal infections was similar between single and bilateral IMAs. There was no difference in long-term survival between the groups. However, in patients with preserved EF, 10-year survival (87.8 versus 75.2%; $P=0.04$) as well as freedom from repeat CABG or MI (86.6% versus 69.05%; $P=0.0086$) were better with bilateral IMAs. There was, however, no survival benefit in those patients with a reduced EF (below 40%). This study implies that diabetic patients with reduced EF and those with comorbidities that accompany reduced EF (e.g., peripheral vascular disease, renal failure) may not benefit from bilateral IMAs. Dissecting only the artery (skeletonization) of the IMA pedicle may decrease the incidence of sternal complications associated with bilateral IMA harvesting.[37] However, there are concerns that skeletonization of the IMA may result in altered endothelial function that may compromise graft patency. So far, this has not been reported, but more long-term follow-up is necessary before the benefits of this technique are established. Nevertheless, as noted from these studies, the use of at least one IMA is crucial to better long-term survival and freedom from recurrent angina in the diabetic CABG patient.

REVASCULARIZATION STRATEGIES FOR PATIENTS WITH DIABETES

See **Table 18-1** and also **Chapter 17**.

Coronary Artery Bypass Graft Surgery versus Percutaneous Transluminal Coronary Angioplasty

The BARI Trial

One of the first trials to compare CABG versus PCI in patients with diabetes mellitus was the Bypass Angioplasty Revascularization Investigation (BARI).[38] Patients were eligible to participate in this trial if they had angiographically documented multivessel coronary artery disease and severe angina or myocardial ischemia that necessitated revascularization that was suitable for both PTCA and CABG. Patients were followed for an average of 5.4 years. The primary endpoint was all-cause mortality at 5 years. Secondary endpoints included MI and functional and symptomatic status. In this trial, 447 patients (24%) had a history of diabetes. Patients with diabetes had a higher prevalence of CHF, hypertension, chronic renal failure, and peripheral vascular disease; reduced EF; and more extensive coronary artery disease. Nevertheless, there was no difference in baseline characteristics between diabetic patients undergoing PTCA versus those undergoing CABG. There was no statistical difference in hospital mortality between diabetic CABG and PTCA patients (1.2% versus 0.6%). Follow-up studies from this trial also investigated the associations between risk factor modification such as statin therapy and glycemic control and clinical outcomes.[39,40]

Nevertheless, at 5 years of follow-up, CABG patients had significantly greater survival than patients assigned to the PCI group (84.4% versus 80.9%; $P=0.043$). The difference in survival entirely involved patients with diabetes. Diabetic

TABLE 18-1 Summary of Clinical Trials on Revascularization for Patients with Diabetes

TRIAL	INCLUSION CRITERIA	ENDPOINTS	RESULTS
BARI I[38]	Multivessel disease necessitating revascularization with targets suitable for either PTCA or CABG	Primary: All-cause mortality at 5 years Secondary: MI, symptomatic status	At 5 years, survival for CABG patients was higher (76.4% versus 55.7%; $P=0.001$). Improvements in survival and freedom from recurrent angina was associated with the use of the IMA.
EAST[42]	Multivessel disease: CABG versus PTCA	Primary: Survival Secondary: Need for repeat revascularization	Survival was greater with CABG versus PTCA. After 8 years, the need for repeat revascularization was greater in PTCA patients (65.3% versus 26.5%; $P<0.001$).
CABRI[43]	Multivessel disease: CABG versus PTCA	Primary: Survival Secondary: Stroke and need for repeat revascularization	At 2 years, nonsignificant increase in survival in CABG patients (96% versus 85%). Composite endpoint of stroke and need for repeat revascularization was lower in CABG patients (11.3% versus 19.1%; $P=0.016$).
ARTS[44]	Multivessel disease: PCI (BMS) versus CABG	Primary: Event-free survival	1-year event-free survival lower in PCI group (63.4% versus 84.4%; $P<0.001$).
SOS[45]	Multivessel disease: PCI (BMS) versus CABG	Primary: Survival	At 6 years, mortality greater in PCI group (10.9% versus 6.8%; $P=0.02$).
CARDIA[47]	Multivessel disease: PCI (BMS, DES) versus CABG	Primary: All-cause mortality, MI, or stroke Secondary: Need for repeat revascularization	1-year combined primary endpoint lower in CABG patients (4.3% versus 19.3%; $P=0.02$).
BARI 2D[39–41]	Multivessel disease: Aggressive medical management versus revascularization with either CABG or PCI (BMS/DES)	Primary: Survival at 5 years Secondary: Composite of death, MI, stroke	No difference in survival between medical therapy versus immediate revascularization. No difference in survival between PCI and CABG. However, CABG patients had a lower incidence of the combined endpoint of death, MI, or stroke (77.6% versus 69.5%; $P=0.01$).
SYNTAX[48]	Multivessel disease: CABG versus PCI (DES)	Primary: Mortality Secondary: Need for repeat revascularization	Repeat revascularization was higher in PCI patients (6.4% versus 20.3%); mortality in more complex lesions was higher in PCI patients (4.1% versus 13.5% ; $P = 0.04$).
FREEDOM[53]	Multivessel disease: CABG versus PCI (DES)	Primary: Composite of all-cause mortality, MI, stroke Secondary: Need for repeat revascularization	5-year primary outcome higher in PCI patients (26.6% versus 18.7%; $P=0.005$). PCI: higher rates of MI (13.9% versus 6%; $P<0.0001$); higher mortality (16.3% versus 10.9%; $P<0.001$); higher need for revascularization at 12 months (13% versus 5%; $P < 0.0001$). Strokes higher in CABG group (5.2% versus 2.4%; $P=0.03$).

ARTS = Arterial Revascularization Therapies Study; BARI = Bypass Angioplasty Revascularization Investigation; BMS = bare metal stent; CABG = coronary artery bypass graft; CABRI = Coronary Angioplasty versus Bypass Revascularization Investigation; CARDIA = Coronary Artery Revascularization in Diabetes trial; DES = drug-eluting stent; EAST = Emory Angioplasty versus Surgery Trial; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SOS = Stent Or Surgery trial; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery study.

patients in the BARI trial (insulin or oral therapy) undergoing CABG surgery had greater survival than patients undergoing PCI (76.4% versus 55.7%; $P=0.0011$). There was no difference in 5-year mortality in the nondiabetic population (86.4% versus 86.8%; $P=0.72$). The excess mortality in diabetic PCI patients was solely a result of cardiac-related issues as opposed to the occurrence of these issues in the CABG group ($P<0.01$). Cardiac mortality was more than three times higher in diabetic patients receiving PCI. In CABG patients, the improvement in survival and freedom from secondary endpoints was associated with the use of IMA grafts. The impact of the IMA graft on cardiac mortality was striking; it was 2.9% when at least one IMA was used versus 8.2% when only saphenous vein grafts were used, the same as that for PCI. The use of the IMA was also associated with a low incidence of post-MI cardiac mortality.

There were several limitations in the BARI trial. The sample size was small. Only 19% of randomized patients (353) had medically treated diabetes mellitus. There was a high crossover rate. Because clinical events generally are higher in diabetic patients, a small trial such as BARI was not adequately powered to show significant differences in clinical outcomes. Finally, patients undergoing PCI predominantly underwent PTCA and did not have the benefits of stents, IIb/IIIa inhibitors, and antiplatelet agents such as clopidogrel. On the other hand, CABG techniques have also improved since the start of the trial. More arterialized grafts are used, the vast majority of CABG patients are on statins, and most receive aggressive perioperative glycemic control. Despite these limitations, the BARI trial revealed that diabetic patients with extensive three-vessel disease are best treated with CABG and the use of at least one IMA graft, rather than PTCA.

In addition to the BARI trial, numerous other studies have compared the effects of CABG versus percutaneous transluminal coronary angioplasty (PTCA) on clinical outcomes. However, too few patients with diabetes mellitus were enrolled to make meaningful conclusions regarding the long-term outcomes of CABG versus PTCA. There were, however, two trials that were adequately powered to assess clinical outcomes. The Emory Angioplasty versus Surgery Trial (EAST) was a single-center, randomized trial in patients with multivessel disease, of whom approximately 25% had diabetes.[42] They were randomized to CABG versus PTCA and followed for 8 years. Although there was no difference in overall survival between the CABG and PTCA groups, survival was greater in diabetic patients who underwent CABG surgery. In the group of patients undergoing PTCA, survival



was significantly better in nondiabetic patients (60.1% versus 82.6%; $P=0.02$). After 8 years, repeat revascularization was necessary in 65.3% of PTCA patients but in only 26.5% of CABG patients ($P<0.001$). The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trial randomized 1054 patients with multivessel disease to either CABG or PTCA.[43] The overall 1-year mortality was no different between CABG (2.7%) and PTCA (3.9%). However, in the 122 randomized patients who had diabetes, there was a nonsignificant trend toward better survival in the CABG group at 2 years (96% versus 85%), a significantly lower incidence of re-revascularization procedures (2.0% versus 11.8%; $P<0.001$), and significantly better relief of angina ($P<0.001$). The overall composite rate of major adverse coronary and cerebral events (MACCEs), which included strokes and the need for repeat revascularization, was significantly lower in CABG patients (11.3% versus 19.1%; $P=0.016$).

Coronary Artery Bypass Graft Surgery versus Percutaneous Coronary Intervention with Bare Metal Stents

The high incidence of restenosis with PTCA led to the emergence of coronary stents. Several trials compared the results of revascularization with CABG versus bare metal stents (BMS). In the Arterial Revascularization Therapies Study (ARTS), a total of 1205 patients were randomly assigned to treatment with PCI or CABG. The event-free survival at 1 year in patients with diabetes was significantly lower in the BMS group (63.4% versus 84.4%; $P<0.001$) because of the higher incidence of repeat revascularization (21.6% versus 12.4%).[44] The difference was largely the result of a lower rate of complete revascularization in patients undergoing PCI with BMS versus CABG (70.5% versus 84.1%; $P<0.001$). Overall, 5-year mortality in patients with diabetes was higher in the BMS group (13.4% versus 8.3%), but this did not reach statistical significance. However, in patients undergoing PCI with BMS, 5-year mortality was higher in patients with versus without diabetes (13.4% versus 6.8%; $P=0.03$) whereas there was no statistical difference in mortality of patients with versus without diabetes in the CABG group (8.3% versus 7.5%; $P=0.8$). In BMS patients, the need for repeat revascularization was significantly higher in patients with versus without diabetes (42.9% versus 27.5%; $P=0.002$). In the Stent Or Surgery (SOS) trial, diabetic patients undergoing CABG had significantly decreased mortality after 6 years compared with patients treated with BMS (10.9% versus 6.8%; $P=0.02$).[45] Hlatky and colleagues analyzed data from 10 randomized trials comparing CABG with PTCA and BMS in 7812 patients.[46] Over a median follow-up of 5.9 years, mortality in patients with diabetes was 30% lower in the CABG group compared with the PCTA and BMS group. In contrast, mortality was increased in diabetic patients undergoing PTCA or BMS (20.0% versus 12.3%; $P=0.014$).

Coronary Artery Bypass Graft Surgery versus Percutaneous Coronary Intervention with Drug-Eluting Stents

In earlier studies comparing CABG versus PCI with PTCA or BMS, the difference in MACCE was driven by the need for repeat revascularization procedures in the PTCA-BMS diabetic patients. It was hoped that the introduction of drug-eluting stents (DESs) with concomitant more aggressive antiplatelet therapy would reduce post-PCI restenosis, stent thrombosis and clinical events and make it a more attractive revascularization option for patients with diabetes mellitus.

The Coronary Artery Revascularization in Diabetes (CARDIA) trial was the first randomized trial of CABG versus coronary stenting using DES in diabetic patients with multivessel disease.[47] In this multicenter study, 510 diabetic patients were randomized to CABG or BMS in earlier phases of the trial, and subsequently in the later phases to DESs. DESs were used in 69% of the PCI group. The primary outcome was the composite of all-cause mortality, MI, or stroke. The secondary outcomes included the need for repeat revascularization. After 1 year, there was no difference in the primary composite outcome (10.5% CABG versus 13.0% PCI; $P=0.39$). However, there was a significant reduction in the combination of the primary endpoint and the need for repeat revascularization in favor of CABG patients (11.3% CABG versus 19.3% PCI; $P=0.02$). The rate of MIs was also significantly higher in the PCI group ($P=0.016$). After 1 year, symptoms had improved in both groups; however, patients randomized to CABG had significantly less angina ($P<0.001$).

BARI 2D

The BARI 2D trial compared aggressive medical management with immediate revascularization using either CABG or PCI versus aggressive medical management alone in patients with diabetes and multivessel CHD.[41] Patients were randomized by the treating physician to either prompt revascularization or medical therapy and then randomized to glucose-lowering treatment with either insulin-sensitizing agents (metformin and/or thiazolidinediones) or insulin providers (sulfonylureas and/or insulin). The primary outcome of the study was survival at 5 years. Secondary endpoints included the composite score of death, MI, or stroke.

Before randomization, the mode of revascularization was determined collaboratively by an interventional cardiologist and a cardiac surgeon. Patients prospectively selected for CABG versus PCI (with BMS and/or DES) had more three-vessel and proximal left anterior descending artery (LAD) disease. By the end of the trial, 42% of patients initially randomized to medical therapy had undergone some type of revascularization procedure. In the primary analysis, there was no statistical difference between the randomized comparator groups of medical therapy versus immediate revascularization for 5-year survival (87.8% versus 88.3%). In a subanalysis of those patients randomized to immediate revascularization, there was no statistical difference in 5-year survival between patients selected for the PCI stratum and those selected for the CABG stratum (88.3% versus 87.8%; $P=0.97$). There was also no difference in secondary endpoints. When compared with medical therapy for all patients, there was no difference in primary or secondary endpoints in patients undergoing PCI. However, a significantly larger number of CABG patients were free from the secondary endpoints of death, MI, or stroke than in the medical treated group (77.6% versus 69.5%; $P=0.01$).

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study compared CABG versus the Taxus Express DES in patients with and without diabetes mellitus and three-vessel disease.[48] After 1 year, the risk of repeat revascularization was higher with DES than CABG in patients with diabetes (6.4% versus 20.3%) or without diabetes (5.7% versus 11.1%). Mortality was higher with

DES, with more complex lesions than in CABG patients (4.1% versus 13.5%). Mack and coworkers compared three-year outcomes of DES with CABG in patients with and without diabetes as part of the SYNTAX trial.[49] MACCE (major adverse coronary and cerebral events) rates were higher in those with versus without diabetes receiving DESs, largely because of an increased need for repeat revascularization. Although diabetes increased MACCE rates among patients receiving DES, the presence of diabetes had little impact on outcomes after CABG. The presence of diabetes significantly increased 3-year MACCE rate, mortality, and need for repeat revascularization in DES patients, but not in patients undergoing CABG. The SYNTAX score is a measure of complexity of the coronary lesion—presence of occlusion, length of the lesion, degree of calcification, and presence of ulceration–with higher scores representing more complex disease. There was no difference in MACCE rate in DES versus CABG in other diabetic or nondiabetic patients with a SYNTAX score below 22. However, in patients with SYNTAX scores higher than 33, the MACCE rate was significantly higher in both diabetic and nondiabetic patients undergoing DES versus CABG. Banning and coworkers further analyzed the MACCE outcomes (death, stroke, MIs, and need for repeat revascularization) in diabetic patients with a SYNTAX score above 33.[48] Overall mortality was significantly increased in patients with DES versus CABG. The need for repeat revascularization was three times higher in DES patients. There was no difference in the incidence of strokes between DES and CABG groups.

Certain subgroups of diabetic patients may also benefit more from particular revascularization strategies. Ohno and colleagues found that in patients with diabetic retinopathy there is a survival benefit of CABG over PCI.[50] Patients with diabetic retinopathy have an increased incidence of CHF and cardiomyopathy, and the results of CABG in this group are especially poor.[51] In a retrospective study of 223 diabetic patients undergoing CABG, Ohno and colleagues found that the 12-year survival was 82% for patients without retinopathy, 56% for patient with mild to moderate, nonproliferative retinopathy, 36% for patients with severe nonproliferative retinopathy, and only 12% for patients with proliferative retinopathy.[52]

Previous trials comparing CABG versus PCI have been criticized because state of the art techniques for PCI or CABG were not used. In an attempt to overcome these limitations, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial used contemporary PCI and CABG techniques and the latest medical therapies, including dual antiplatelet agents, to determine whether CABG or PCI with DES is the optimal method to revascularize patients with diabetes mellitus who have multivessel coronary disease.[53] The study prospectively randomized 1900 patients with diabetes mellitus and multivessel disease to either CABG or PCI with DES at 140 centers throughout the world from 2005 to 2010. The primary outcome was a composite of all-cause mortality, nonfatal MI, and nonfatal stroke. After 5 years, the incidence of the primary outcome was 26.6% in the PCI group—significantly higher than in patients undergoing CABG (18.7%; $P=0.005$). PCI patients also had a significantly higher rate of MIs (13.9% versus 6%; $P<0.0001$) and experienced a higher overall mortality (16.3% versus 10.9%; $P<0.001$). The incidence of stroke was higher in the CABG group (5.2% versus 2.4%; $P=0.03$), mainly because of an increased rate of events in the first 30 days after surgery. These results were independent of the SYNTAX score. At 12 months, PCI patients required significantly more repeat revascularization procedures (13% versus 5%; $P<0.0001$). The FREEDOM trial adds further support to the premise that in diabetic patients with multivessel disease, CABG is the preferred method for coronary revascularization.

The Optimal Strategy for Coronary Revascularization in Patients with Diabetes and Multivessel Coronary Artery Disease (Fig. 18-1 and also see Chapter 17)

The BARI 2D trial demonstrated that for patients with diabetes mellitus and stable multivessel coronary artery disease, optimal medical therapy rather than immediate revascularization with PCI or CABG is an appropriate and effective first-line strategy.[39] In patients in whom medical therapy has failed and who have left main and severe multivessel disease, CABG appears to offer the best therapy. It results in better long-term survival, freedom from recurrent MIs, and need for repeat revascularization.[54–56] CABG offers more complete revascularization, especially in patients with more

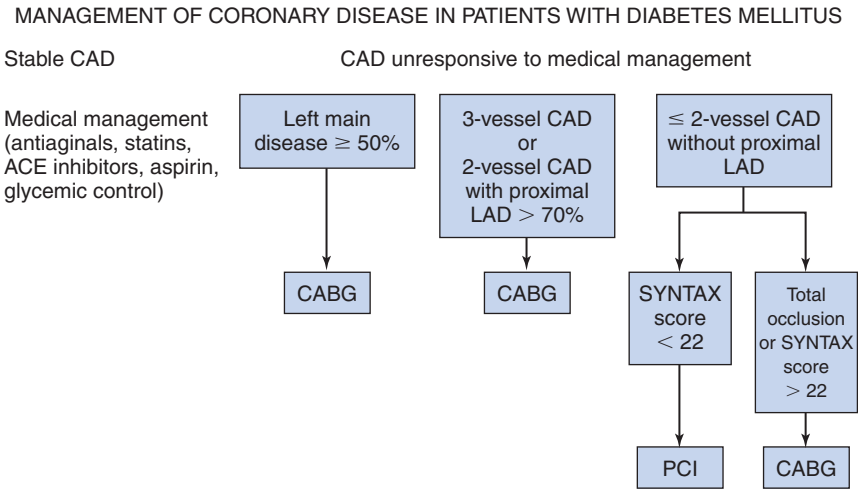


FIGURE 18-1 Management of coronary disease in patients with diabetes mellitus. ACE = Angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial.



complex and severe three-vessel disease (SYNTAX score above 22). In the BARI trial, CABG patients received an average of 3.1 grafts versus 2.0 lesions treated by PCI. This resulted in larger areas of unprotected and jeopardized myocardium and helps to explain the increased incidence of MIs, need for revascularization, and decreased survival seen in the PCI-treated patients.

Some may argue that results of PCI for patients with diabetes are improving with the use of stents, antiplatelet agents, antithrombotic agents, and glucose-lowering drugs (see also **Chapter 17**).[57–59] However, CABG techniques have also improved.[60,61] Most important, the concept of glycemic control in the perioperative period has now emerged as an important adjuvant therapy in the diabetic patient undergoing CABG surgery.[62]

HYPERGLYCEMIA IN PATIENTS WITH DIABETES UNDERGOING CORONARY ARTERY BYPASS GRAFT SURGERY

Detrimental Effects of Hyperglycemia in the Diabetic Myocardium and its Reversal with Insulin

The primary energy substrate for the nonischemic myocardium is free fatty acids.[63] However, during periods of ischemia, glucose is the preferred myocardial energy substrate (also see **Chapter 24**). This allows the ischemic myocardium to more efficiently use oxygen to generate the ATP necessary to preserve cellular transport systems needed to preserve cellular integrity and ultimately contractile function. However, the diabetic myocardium has impaired glucose oxidation because of impaired transport into the myocyte and decreased endogenous insulin secretion, all of which contribute to hyperglycemia.[64] Hyperglycemia results in the formation of advanced glycation end-products (AGEs) and ligand activation of the cell surface receptor (RAGE), which activates three proinflammatory transcription factors normally suppressed by insulin: nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and early growth response protein 1 (EGR-1),[65–67] which are responsible for activating pathways leading to vascular inflammation and oxidative stress (also see **Chapter 9**).[68] The protein kinase C pathway is activated, which results in decreased endothelial nitric oxidase synthase and increased levels of the potent myocardial vasoconstriction endothelin-1 (also see **Chapter 10**).[69] This altered endothelial function during CABG contributes to perioperative ischemic necrosis and altered graft patency. Bioassays from IMA and saphenous vein grafts taken from diabetic CABG patients show decreased nitric oxide activity and increased production of superoxide radicals compared with nondiabetic patients.[70,71] Activation of the protein kinase C pathway also leads to activation of prothrombotic factors and promotes adhesiveness and hyperaggregability of platelets. This predisposes to coronary thrombosis, which ultimately affects long-term vein graft patency and plays a major role in the increased incidence of MIs, recurrent angina, and need for revascularization procedures in diabetic patients.[72,73]

Insulin enhances myocardial glucose metabolism by facilitating glucose transport into the myocyte, inhibiting the release of free fatty acids, and augmenting aerobic metabolism by stimulating pyruvate dehydrogenase.[74] It acts as an anti-inflammatory agent by suppressing proinflammatory transcription factors, reduces inflammatory mediators, enhances endothelial function by upregulating the L-arginine nitric oxide pathway and improves platelet function by decreasing plasminogen activator 1.[75–77] In clinical studies, insulin has been shown to decrease levels of free fatty acids after CABG, improve aerobic metabolism when added to cardioplegic solutions, and decrease the level of reactive oxygen species, adhesion molecules, and C-reactive protein.[78–80]

Effect of Hyperglycemia on Morbidity and Mortality in Coronary Artery Bypass Graft Patients

Hyperglycemia is associated with increased morbidity and mortality in both diabetic and nondiabetic patients undergoing CABG surgery. Doenst and coworkers found that patients with glucose levels above 360 mg/dL during CABG had a higher incidence of morbidity and mortality irrespective of whether they were known to have diabetes mellitus.[81] Mortality was three times higher in patients with hyperglycemia. Fish and coworkers found that elevated postoperative serum glucose levels (>250 mg/dL) were associated with a 10-fold increase in complications in CABG patients.[82] Similar findings in increased postoperative morbidity associated with elevated perioperative glucose levels were noted by McAlister and colleagues,[83] Imran and colleagues,[84] Székely and colleagues,[85] and Duncan and colleagues.[86] Mean glucose levels exceeding 200 mg/dL in the postoperative period are also an increased risk factor for sternal wound infections and mediastinitis.[87,88] Abnormal glucose values before surgery may also be predictive of decreased survival after surgery. Anderson and coworkers found that CABG patients with impaired fasting glucose levels had double the 1-year mortality rate.[89] Imran and coworkers noted a strong correlation between elevated admission blood glucose and increased morbidity following CABG.[84] Fluctuations in variability in intraoperative and postoperative blood glucose levels have also been associated with increased morbidity and mortality after all types of cardiac surgery procedures.[86] These studies strongly suggest that patients with and without diabetes mellitus with elevated blood glucose values in the perioperative period after CABG and cardiac surgery have increased short- and long-term morbidity and mortality.

Effects of Insulin Infusions in the Diabetic Coronary Artery Bypass Graft Surgery Patient

One of the earliest studies to show the beneficial effects of insulin in diabetic patients with ischemic heart disease was the Diabetes and Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial.[90] In this trial, which involved 620 patients with acute MI, patients were prospectively randomized to receive an intravenous (IV) glucose insulin infusion followed by multidose subcutaneous insulin injections. Patients treated with the DIGAMI protocol had a 30% reduction in mortality over 1 year that persisted for a mean of 3.5 years.[91] Lazar and coworkers used a similar solution (500 mL D_{5W} plus 80 units regular insulin plus 40 mEq potassium chloride [KCl]), designed to keep serum glucose below 180 mg/dL to determine whether glycemic control would also limit ischemic damage in diabetic patients undergoing CABG surgery.[92] In this prospective randomized trial involving 141 CABG patients, the control group received

a sliding-scale insulin coverage targeted to keep serum glucose below 250 mg/dL. The insulin infusions were initiated on anesthetic induction and continued for 12 hours in the ICU. Patients receiving the insulin infusions achieved better glycemic control in the operating room and in the initial 12 hours after surgery. They had significantly lower serum lactate and free fatty acid levels. Although these favorable metabolic changes did not result in any difference in mortality (0% for each group), they were reflected in a decrease in postoperative morbidity and improved long-term survival. Patients treated with tight glycemic control had significantly higher cardiac indices and less need for inotropic support. They gained less weight and spent less time on the ventilator. They had a lower incidence of infections (0% versus 13%; $P=0.01$) and atrial fibrillation (15% versus 60%; $P=0.007$), which all contributed to a shorter hospital length of stay (6.5 versus 9.2 days; $P=0.0003$). After 5 years of follow-up, patients achieving tight glycemic control had a significantly lower incidence of recurrent ischemia, a lower angina class, and significantly increased survival ($P=0.04$). This study showed the importance of use of continuous insulin infusions as opposed to intermittent subcutaneous insulin to achieve glycemic control (120 mg/dL to 180 mg/dL) in diabetic CABG patients. It also showed that tight glycemic control not only improved short-term perioperative outcomes, but also increased long-term survival and reduced recurrent ischemic events. Another observational study suggesting the benefits of tight glycemic control during cardiac surgery was reported by Furnary and coworkers.[93] In 3554 patients undergoing CABG surgery from 1987 to 2001, continuous insulin infusions in which the "Portland Protocol" was used to keep serum glucose between 100 and 150 mg/dL resulted in significantly lower mean glucose levels that could not be achieved with intermittent subcutaneous insulin therapy. This was associated with a 50% reduction in operative mortality in CABG patients with diabetes mellitus, along with a significant decrease in the incidence of deep sternal wound infections. In a follow-up observational study using the Portland Protocol, Furnary and coworkers assessed glycemic control using a formula called 3-BG, which consisted of the average of all glucose values obtained on the day of surgery and the first and second postoperative days.[94] An increase in 3-BG was found to be an independent predictor of perioperative mortality, deep sternal wound infections, atrial fibrillation, low cardiac output syndrome, and hospital length of stay.

Sternal wound infections are a significant source of morbidity and mortality in diabetic CABG patients and are more likely to occur when the serum glucose exceeds 200 mg/dL in the perioperative period.[87] Kerr and coworkers found that the incidence of sternal infections in diabetic CABG patients increased from 1.3% to 6.7% when glucose values exceeded 250 mg/dL.[88] Maintaining patients on a continuous insulin infusion with mean glucose values of 100 to 150 mg/dL significantly decreased the incidence of sternal infections. Hruska and coworkers were able to significantly decrease the incidence of sternal infections in diabetic CABG patients by maintaining glucose levels between 120 and 160 mg/dL using continuous insulin infusions.[95] Improved phagocytic function in the neutrophils of diabetic cardiac surgical patients may be the mechanism responsible for the reduced incidence of wound infections with insulin infusions. Rassias and coworkers found in a prospective randomized study of diabetic cardiac surgical patients that neutrophil phagocytic activity was better preserved in those patients on a continuous insulin drip than in those receiving only intermittent boluses of insulin used to treat perioperative hyperglycemia.[96]

The importance of tight glycemic control during CABG was also noted by van den Berghe and colleagues in a prospective, randomized study involving 1548 ventilator patients admitted to an ICU, of whom 62% had undergone cardiac surgery and 13% had a prior history of diabetes mellitus.[97] Patients were randomized to a conventional group in which insulin was administered intermittently when serum glucose exceeded 250 mg/dL to maintain a goal of 180 to 200 mg/dL versus an intensive group receiving a continuous insulin infusion to maintain glucose levels between 80 and 110 mg/dL. Intensive insulin therapy resulted in a significant reduction in mortality (10% versus 20%; $P=0.005$) in those patients who required 5 or more days of ICU care and had multiorgan failure and sepsis. Cardiac surgical mortality was reduced in only those patients who required 3 or more days of ICU care. In another attempt to identify patients who might benefit most from tight glycemic control, D'Alessandro and coworkers compared outcomes in diabetic patients treated with intermittent subcutaneous insulin infusions to maintain serum glucose between 150 and 200 mg/dL versus those treated with a continuous insulin infusion titrated to keep serum glucose below 150 mg/dL.[98] Clinical outcomes were correlated with EuroSCORE risk profiles, which include age, urgency of surgery, EF, and other comorbidities. Patients with the highest predicted EuroSCORE had significantly lower observed mortality when glycemic control was achieved with continuous insulin infusions. These results and the findings of van den Berghe and colleagues strongly suggest that diabetic patients with the highest risk tend to benefit most from tight glycemic control.

What is the Optimal Target for Serum Glucose in the Diabetic Coronary Artery Bypass Graft Surgery Patient—Aggressive or Moderate Control?

The data presented in this chapter demonstrate that tight glycemic control improves outcomes in diabetic patients undergoing CABG surgery. However, the optimal target for perioperative serum blood glucose is unknown. Studies have shown that maintaining serum glucose below 180 mg/dL reduces morbidity and mortality in CABG patients. However, the effects of more aggressive control on clinical endpoints are less clearly defined. Recent trials in ICU and non-ICU surgical and nonsurgical patients have raised concerns that more aggressive glycemic control toward normalization of blood glucose values may actually increase mortality.[99–102]

To determine the effects of more aggressive glycemic control in diabetic patients during CABG surgery, Lazar and coworkers prospectively randomized patients to either an aggressive (target blood glucose 90 to 120 mg/dL) or a moderate (blood glucose targets 120 to 180 mg/dL) protocol.[103] There was no difference in the incidence of 30-day mortality, MI, neurologic events, deep sternal infections, or atrial fibrillation between the groups. Patients with aggressive control had a higher incidence of hypoglycemic events, but this did not result in any evident clinical sequelae. Hence, more aggressive glycemic control did not result in any significant improvement in clinical outcomes that could not be

achieved with more moderate control. These results were consistent with a study by Bhamidipati and coworkers that showed that achievement of glycemic control (120 to 179 mg/dL) in diabetic CABG patients was associated with the least amount of morbidity and mortality.[104] The American College of Physicians now recommends achieving a more moderate glucose level of 140 to 200 mg/dL in surgical and medical ICU patients.[105]

There are several explanations why more aggressive protocols to achieve glycemic control fail to enhance clinical outcomes. Many patients were already receiving optimal cardiovascular prevention with statins, angiotensin-converting enzyme inhibitors, aspirin, and weight-reduction programs. Therefore the added benefit of more aggressive glucose control may not have been as significant in these patients. Furthermore, moderate control has already been shown to significantly improve clinical outcomes in CABG patients, which may be difficult to improve on with a more aggressive protocol. Although more aggressive control did not improve short-term outcomes, it did lower markers of inflammation such as free fatty acids.[103] It is conceivable that this reduction in the inflammatory response may result in improved long-term outcomes by enhancing vein graft patency. Additional studies will be needed to determine the most optimal level of glycemic control in the diabetic patient undergoing CABG surgery.

Management of Hyperglycemia in the Perioperative Period

Achieving glycemic control in the perioperative period requires a multidisciplinary approach that includes representation from nursing, anesthesiology, pharmacy, surgery, and endocrinology.[106] At our institution, we formed a Perioperative Glycemic Control Committee, which has resulted in serum glucose levels below 180 mg/dL in the first 48 hours in 94% of all cardiac surgery patients.[107]

Glycemic control in the diabetic cardiac surgical patient is best achieved with strategies that are instituted in the preoperative period (**Box 18-1**). All patients should have hemoglobin A1c (HbA1c) level assessed before surgery. Obtaining an HbA1c level before surgery from diabetic patients and those patients at risk for postoperative hyperglycemia helps to optimize glycemic control in patients with elevated HbA1c levels. IV insulin is the preferred method of insulin delivery to achieve rapid and effective glycemic control in hospitalized patients who are hyperglycemic before surgery.[108] It is important to identify all patients with abnormal renal function because the risk for hypoglycemia is increased in all of these patients.[109]

It is important to realize that insulin resistance increases during surgery but then rapidly decreases in the postoperative period (**Box 18-2**). This results in an intraoperative rise in insulin requirements followed by a rapid fall in the immediate postoperative period. This is caused by hypothermia, the increased glucose load associated with cardioplegia delivery, the glucose used to prime the cardiopulmonary bypass circuit, and the need for inotropic support.[110] After discontinuation of cardiopulmonary bypass, when these factors are no longer present, insulin requirements decrease rapidly; if this is unrecognized, severe hypoglycemia can result.[111]

In the ICU, all patients should have serum glucose levels below 180 mg/dL (**Box 18-3**). Multiple protocols for ICU continuous insulin infusions have been established.[112–114] An example of the protocol used at the Boston Medical Center is shown in **Figure 18-2**. Recently, computer-based algorithms have become commercially available to assist the nursing staff in adjusting insulin infusion rates.[115,116] Although studies have shown that computer-based algorithms have been associated with tighter glucose control, there have been no reported differences in the frequency of hypoglycemic events, length of ICU and hospital stay, or mortality with these algorithms; their use depends on physicians' preferences and cost considerations.[117–119]

The following are the current recommendations of the Society of Thoracic Surgeons regarding blood glucose management during adult cardiac surgery[120]:

- All patients with diabetes undergoing cardiac surgical procedures should receive an insulin infusion in the operating room and for at least 24 hours postoperatively to maintain serum glucose levels below 180 mg/dL. (Class I; level of evidence B)
- HbA1c levels should be obtained before surgery in patients with diabetes and in patients at risk for postoperative hyperglycemia to characterize the level of postoperative glycemic control. (Class I; level of evidence C)

BOX 18-1 Perioperative Glucose Management in the Preoperative Period

Hemoglobin A1c (HbA1c) level is obtained from *all* cardiac surgery patients
Oral hypoglycemic medications are discontinued 12 hours before surgery
Patients on insulin at home:
 Reduce NPH insulin by one half to one third
 Continue basal insulin dose (glargine)
Hospitalized patients with hyperglycemia (>180 mg/dL) receive an intravenous insulin drip

BOX 18-2 Contributors to Perioperative Hyperglycemia and its Management

Underlying insulin resistance
Hypothermia
Cardiopulmonary bypass
Cardioplegia solutions
Inotropes
Rewarming

Check glucose levels *immediately before* transfer to the intensive care unit
Administer intravenous insulin drip for *persistent* glucose levels above 180 mg/dL
Monitor glucose levels:
 q30-60 min
 q15min during periods of rapid fluctuation

BOX 18-3 Perioperative Glucose Management in the Intensive Care Unit

All patients, with and without diabetes mellitus, with *persistent* glucose levels above 180 mg/dL receive continuous insulin infusions to maintain serum glucose below 180 mg/dL for the *duration of ICU care.* (Class I; level of evidence A)
All patients who require 3 or more days in the ICU because of:
 Need for inotropes
 Intraaortic Balloon Pump or Left Ventricular Assist Device Support
 Antiarrhythmics
 Renal replacement therapy
Receive a continuous insulin infusion to maintain blood glucose below 150 mg/dL, *regardless* of their diabetic status. (Class I; level of evidence B).
Glucose values are monitored hourly while the patient is on an insulin drip and every 15 minutes when serum glucose levels are 70 mg/dL or below.

120–180 mg/dL Insulin Infusion Guideline
Not to be used in patients in acute diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome

Goal: The goal is to maintain whole blood glucose levels and/or finger sticks between 120 and 180 mg/dL.

Revised 03/10

	Below desired range		*Desired range*	*Above desired range*					
Glucose level	<80 mg/dL	80–119 mg/dL	120–180 mg/dL (see example end of page)	181–220 mg/dL	221–250 mg/dL	251–300 mg/dL	301–350 mg/dL	>351–400 mg/dL	>400 mg/dL
Infusion rate of ≤1 unit/hr	D/C infusion: give 25 cc of D50 IVP	Decrease infusion by 0.5 unit/hr	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 0.5 unit/hr*	↑Infusion by 1 unit/hr	Give 2 units insulin IVP and ↑infusion by 1 unit/hr	Give 3 units insulin IVP and ↑infusion by 1 unit/hr	Give 4 units insulin IVP and ↑infusion by 1 unit/hr	Give 6 units insulin IVP and ↑infusion by 1 unit/hr	*Call MD*
Infusion rate of 2–5 units/hr	*Call MD* √ glucose level in 30 min. If >120 mg/dL, restart at ½ previous rate. Resume q 1 hr fingersticks until stable. Restart drip as above *any time* glucose is >120 mg/dL.	Decrease infusion by 1 unit/hr	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 0.5 unit/hr*	↑Infusion by 1 unit/hr	Give 2 units insulin IVP and ↑infusion by 1 unit/hr	Give 3 units insulin IVP and ↑infusion by 1 unit/hr	Give 6 units insulin IVP and ↑infusion by 1 unit/hr	Give 8 units insulin IVP and ↑infusion by 1 unit/hr	
Infusion rate of 6–10 units/hr		Decrease infusion by 2 units/hr	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 1 unit/hr	↑Infusion by 1.5 units/hr	Give 2 units insulin IVP and ↑infusion by 2 units/hr	Give 3 units insulin IVP and ↑infusion by 2 units/hr	Give 6 units insulin IVP and ↑infusion by 2 units/hr	Give 8 units insulin IVP and ↑infusion by 2 units/hr	
Infusion rate of 11–15 units/hr		Decrease infusion by 3 units/hr	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 2 units/hr*	↑Infusion by 2 units/hr	Give 2 units insulin IVP and ↑infusion by 3 units/hr	Give 3 units insulin IVP and ↑infusion by 3 units/hr	Give 6 units insulin IVP and ↑infusion by 3 units/hr	Give 8 units insulin IVP and ↑infusion by 3 units/hr	
Infusion rate of >16 units/hr				*Call MD*					

Monitoring:
* "Once in range" example

Check glucose q1h until stable (blood glucose remains in desired range for 3 consecutive measurements) then reduce checks to q2h. Blood sugars should be checked AT LEAST EVERY 2 HOURS while a patient is on an insulin infusion.

Glucose	190	140 (in range now)	130 (drop #1)	120 (drop #2)	130
Units/hr	4	4	4	↓3.5	3.5

FIGURE 18-2 Example of perioperative continuous insulin infusion protocol.

- Glucose levels above 180 mg/dL that occur in patients without diabetes only during cardiopulmonary bypass may be treated initially with a single intermittent dose of IV insulin as long as the levels remain below 180 mg/dL. However, in those patients with persistently elevated glucose (above 180 mg/dL) after cardiopulmonary bypass, a continuous insulin drip should be instituted. (Class I; level of evidence B)
- Patients with and without diabetes with persistently elevated serum glucose (above 180 mg/dL) should receive IV insulin infusions to maintain serum glucose below 180 mg/dL for the duration of their ICU care. (Class I; level of evidence A)
- All patients who require 3 or more days in the ICU because of ventilatory dependency and who require inotropes, Intraaortic Balloon Pump or LV assist device support, antiarrhythmics, dialysis, or continuous venovenous hemofiltration should have a continuous insulin infusion to keep glucose levels at or below 150 mg/dL, regardless of their diabetic status. (Class I; level of evidence B)

Glycemic Control after the Intensive Care Unit

When patients are ready to be discharged from the ICU, glycemic control can be achieved by a combination of long- and rapid-acting subcutaneous insulin agents (**Figure 18-3**). Patients are ready to be transitioned to a

EXAMPLE TRANSITION FROM CONTINUOUS INSULIN INFUSION TO SUBCUTANEOUS INSULIN THERAPY

A patient with type 2 diabetes has required 1.5 units per hour on an insulin drip from 3 am to 6 am and has just started to eat a regular carbohydrate-controlled diet. There is no dextrose infusion, inotrope or pressor therapy. Insulin orders:

1) Glargine insulin dose = 1.5 × 2 = 30 units. "30 units subcutaneous × 1 now. Discontinue insulin infusion 2 hours after this injection."
2) Lispro insulin 6 units three times a day with meals (this dose may be titrated up to nine units with meals as necessary). Inject 15 minutes before or after first bite. Hold if missed meal, NPO, or if glucose <70 mg/dL.
3) Rapid-acting insulin correction scale as needed with scheduled meal insulin, at bedtime, and overnight. Add to scheduled insulin dose if patient is eating, or give alone to correct glucose if patient not eating:

Glucose	Dose
140–190	2 units
191–240	4 units
240–290	6 units
> 290	8 units

FIGURE 18-3 Example transition from continuous insulin infusion to subcutaneous insulin therapy.

BOX 18-4 Perioperative Glucose Management after the Intensive Care Unit

Target Goals
Blood glucose <180 mg/dL in postprandial state
Blood glucose 100-140 mg/dL in fasting and premeal states
Goals are best achieved with subcutaneous insulin combining intermediate- and rapid-acting insulin agents.
Oral agents are resumed when target glucose levels are maintained and the patient is tolerating a normal diet.
Metformin should *not* be restarted until the patient is documented to have normal renal function.

scheduled basal insulin regimen when they meet the following criteria:

- A stable IV insulin infusion rate is maintained for at least 4 hours in the fasting state.
- The patient is extubated and off pressor agents.
- The patient is ready to receive oral, enteral, or parenteral nutrition.[107]

Our goals during the non-ICU phase of the patient's hospital stay are as follows (**Box 18-4**):

- Target a blood glucose level below 180 mg/dL in the postprandial state.
- Achieve a blood glucose level of 100 to 140 mg/dL in the fasting and premeal states after transfer to the floor.

The best method to achieve consistent glycemic control in clinically stable patients with diabetes is with scheduled basal or bolus insulin therapy. This is accomplished best with subcutaneous insulin that combines long- or intermediate-acting insulin with rapid-acting insulin administered simultaneously with nutritional intake.

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PART IV

EPIDEMIOLOGY AND MANAGEMENT OF ACUTE CORONARY SYNDROMES IN PATIENTS WITH DIABETES

19 Epidemiology of Acute Coronary Syndromes in Patients with Diabetes

Anselm K. Gitt

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GLOBAL BURDEN OF CARDIOVASCULAR DISEASE AND DIABETES

Cardiovascular diseases are the number one cause of death worldwide.[1] In 2008, approximately 17.3 million people died from cardiovascular disease, accounting for approximately one third of all deaths; an estimated 7.3 million were caused by coronary heart disease and another 6.2 million by stroke.[2] Until recently, cardiovascular diseases were more frequent in the developed countries, but during the past years low- and middle-income countries have been disproportionally affected. According to the 2010 Global Status Report of the World Health Organization on noncommunicable diseases, over 80% of cardiovascular disease deaths take place in low- and middle-income countries, with no differences between men and women,[1] predominantly as a result of ischemic heart disease (**Fig. 19-1**).[2] Furthermore, the number of people who die from cardiovascular diseases will increase to reach 23.3 million by 2030; ischemic heart disease will remain the single leading cause of death in 2030 (**Fig. 19-2**).[3]

The most important behavioral risk factors of cardiovascular diseases are unhealthy diet, physical inactivity, and tobacco use. These may contribute to raised blood pressure, abnormal blood lipids, raised blood glucose, and overweight and obesity. The increasing frequencies of obesity and sedentary lifestyles—major risk factors for the development of type 2 diabetes, in both developed and developing countries—will further contribute to diabetes being a growing clinical and public health problem worldwide.

The International Diabetes Federation (IDF) reports that 371 million people had diabetes in 2012 (see also **Chapter 1**). The worldwide prevalence of diabetes was 8.4% in the population aged 20 to 79 years, including an estimated 50% (29.2% to 81.2%) of whom had undiagnosed diabetes; there were large differences in prevalence and proportions diagnosed among different regions and countries worldwide (**Fig. 19-3**).[4]

In 2012, 4.8 million people died from complications of diabetes mellitus.[4] In the ranking of causes of death, diabetes will move from rank 11 in the year 2002 to rank 7 in 2030 (**Table 19-1**).[3]

INTERHEART,[5] a large-scale standardized, case-control study involving 15,152 patients with acute myocardial infarction and 14,820 controls, examined the relationship between important cardiovascular risk factors, such as hypertension, diabetes mellitus, and lifestyle, and myocardial infarction in 52 countries worldwide. The study identified diabetes mellitus to be associated with a more than doubled adjusted odds for the development of myocardial infarction (odds ratio [OR] 2.37, 95% confidence interval [CI] 2.07-2.71) for the overall population after adjustment for all other risk factors.[5]

In a population-based study in Denmark, all 3.3 million inhabitants at least 30 years of age and older were identified through the Danish Civil Registration System and followed for 5 years from 1997 to 2002 by individual-level linkage of nationwide registers to estimate cardiovascular risk associated with diabetes mellitus.[6] Diabetes patients receiving glucose-lowering medications and individuals without diabetes, both with and without prior myocardial infarction,

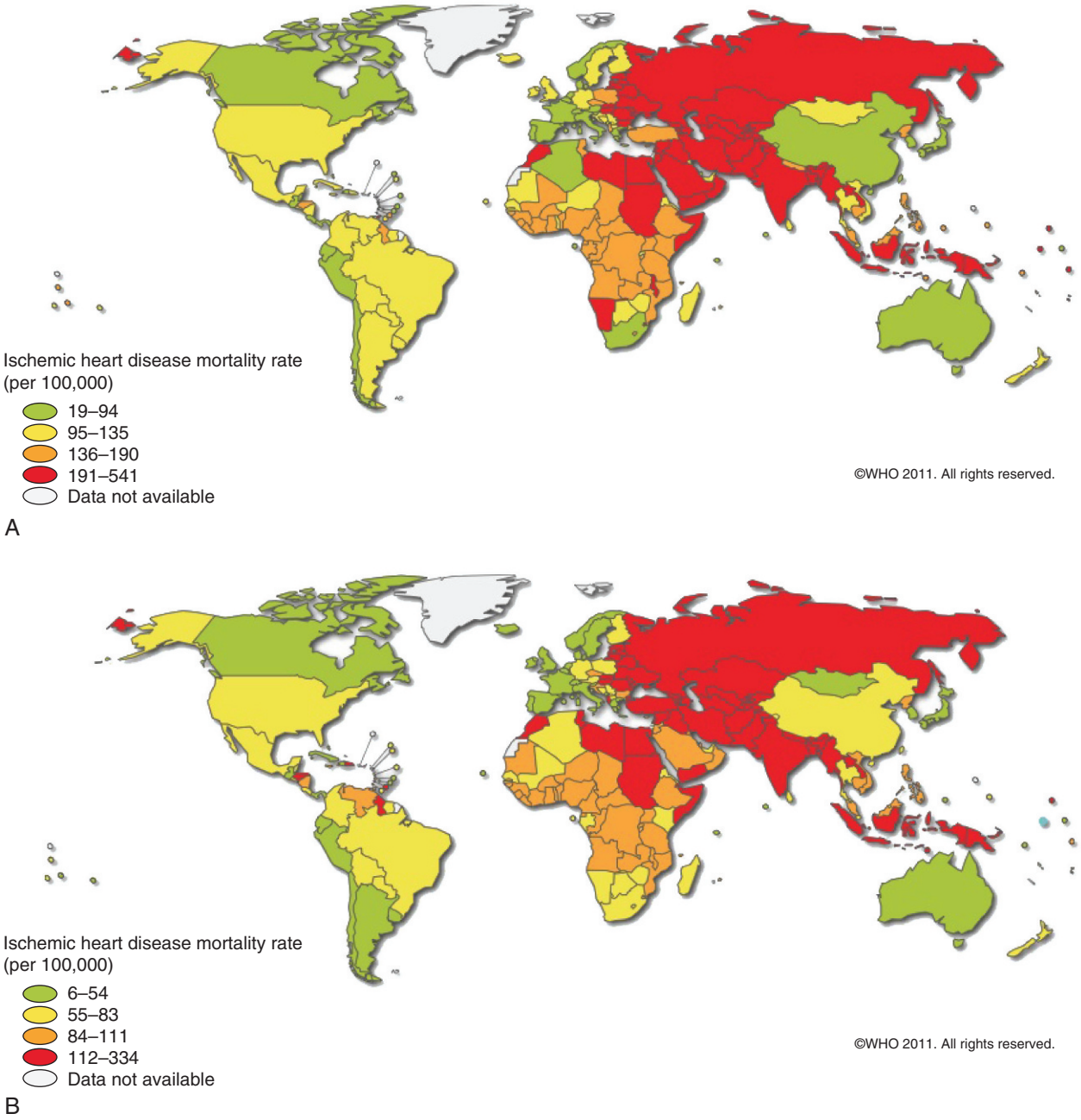


FIGURE 19-1 Global distribution of age standardized ischemic heart disease mortality rates (per 100,000) in men (A) and women (B). *(Data from Mendis S, Puska P, Norrving B, eds: Global atlas on cardiovascular disease prevention and control. Geneva, Switzerland, 2011, World Health Organization (WHO). Available at http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf.)*

were compared. Regardless of age and sex the hazard ratios (HRs) for cardiovascular death were as high in patients with diabetes mellitus without prior myocardial infarction as in nondiabetic patients with prior myocardial infarction (HR in men 2.42 and 2.44, respectively, and $P=0.60$; HR in women 2.45 and 2.62, respectively, and $P<0.001$; **Fig. 19-4**).[6] Based on these data, diabetes mellitus might be seen as a coronary artery disease risk equivalent. The incidence rates of myocardial infarction during the 5 years of follow-up in this study in men and women with diabetes and without prior myocardial infarction were 7.3% and 6.9%, respectively; for those with diabetes and prior myocardial infarction, the incidence rates were 23.7% and 25.0%, respectively (**Table 19-2**, **Fig. 19-5**).[6]

Further population-based studies with long-term follow-up describing the prevalence of acute coronary syndromes (ACSs) in patients with diabetes are lacking. Available data on patients with diabetes are heterogeneous, because diabetic patients with a long duration of the disease have a different cardiovascular risk than patients with shorter disease duration. The type of diabetes treatment—that is, insulin versus noninsulin—also correlates with risk for ACS, most likely reflecting differences in underlying disease severity. In the ideal setting, information regarding the long-term risk of a patient with newly diagnosed diabetes mellitus for coronary artery disease and its complications would be desirable, but data on the long-term risk of cardiovascular events for patients with new onset of diabetes are scarce. This

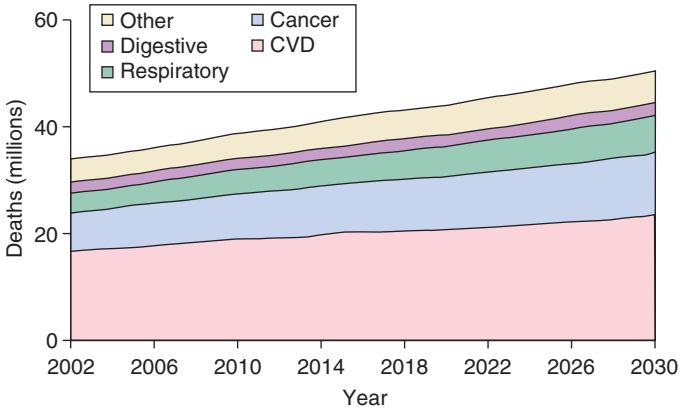


FIGURE 19-2 Projection of global deaths from different underlying diseases through 2030. In 2030 there will be approximately 23 million deaths caused by cardiovascular diseases. CVD = Cardiovascular disease. *(Modified from Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030, PLoS medicine 2006;3:e442.)*

information could be obtained only if patients were prospectively followed from the time of their first diagnosis of diabetes mellitus. In theory, such an approach would be possible in countries where civil registration systems can be matched with, for example, prescription registries, allowing the identification of patients in whom glucose lowering treatment has been initiated.

Although population-based studies on the prevalence of ACSs in patients with diabetes are scarce, data from randomized controlled trials (RCTs) as well as from prospective observational studies such as surveys and registries in the ACS setting provide some further insights.

TABLE 19-1 Projected Changes in Rankings for 15 Leading Causes of Death, 2002 and 2030

CATEGORY	DISEASE OR INJURY	2002 RANK	2030 RANK	CHANGE IN RANK
Within top 15	Ischemic heart disease	1	1	1
	Cerebrovascular disease	2	2	0
	Lower respiratory infections	3	5	−2
	HIV/AIDS	4	3	+1
	COPD	5	4	+1
	Perinatal conditions	6	9	−3
	Diarrheal diseases	7	16	−9
	Tuberculosis	8	23	−15
	Tracheal, bronchial, lung cancers	9	6	+3
	Road traffic accidents	10	8	+2
	Diabetes mellitus	11	7	+4
	Malaria	12	22	+10
	Hypertensive heart disease	13	11	+2
	Self-inflicted injuries	14	12	+2
	Stomach cancer	15	10	+5
Outside top 15	Nephritis and nephrosis	17	13	+4
	Colon and rectum cancers	18	15	+3

Ischemic heart disease will remain the number one cause of death. Diabetes will move from rank 11 to rank 7 in 2030.

AIDS = Acquired immunodeficiency syndrome; *COPD* = chronic obstructive pulmonary disease; *HIV* = human immunodeficiency virus.

Data from Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030, *PLoS Med* 3:e442, 2006.

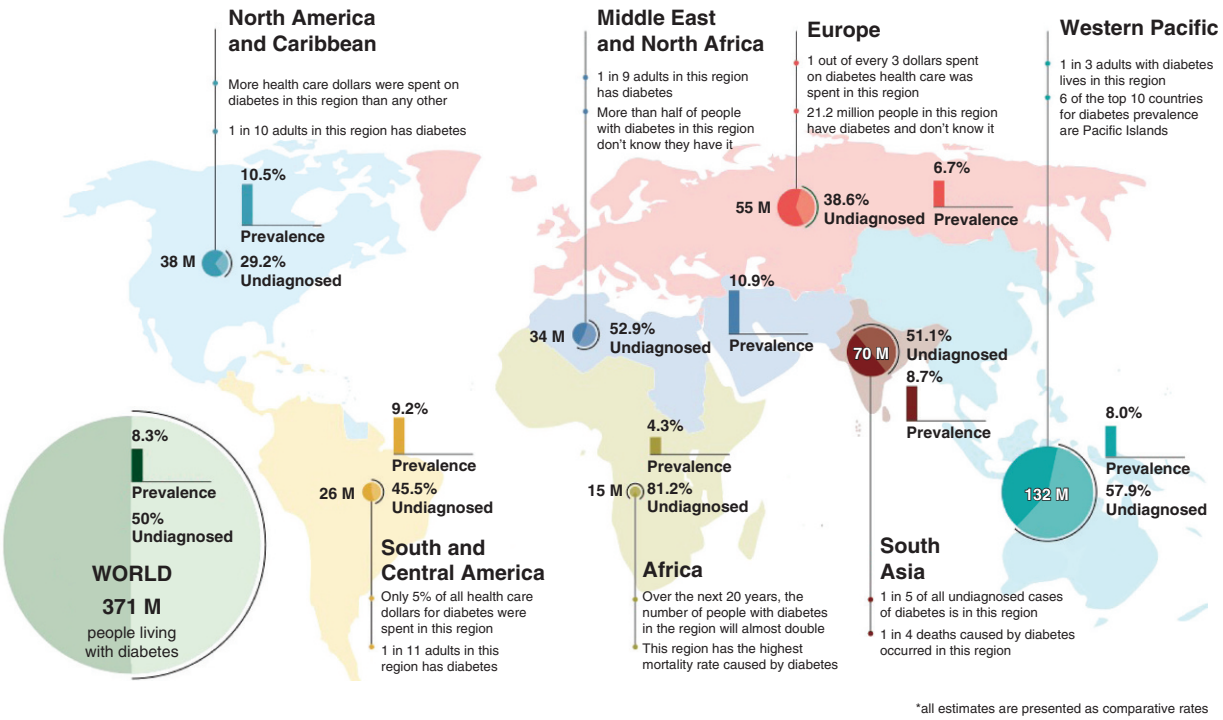


FIGURE 19-3 Global prevalence of diagnosed and undiagnosed diabetes. *(Modified from International Diabetes Federation Diabetes Update 2012. At www.idf.org/diabetesatlas.)*

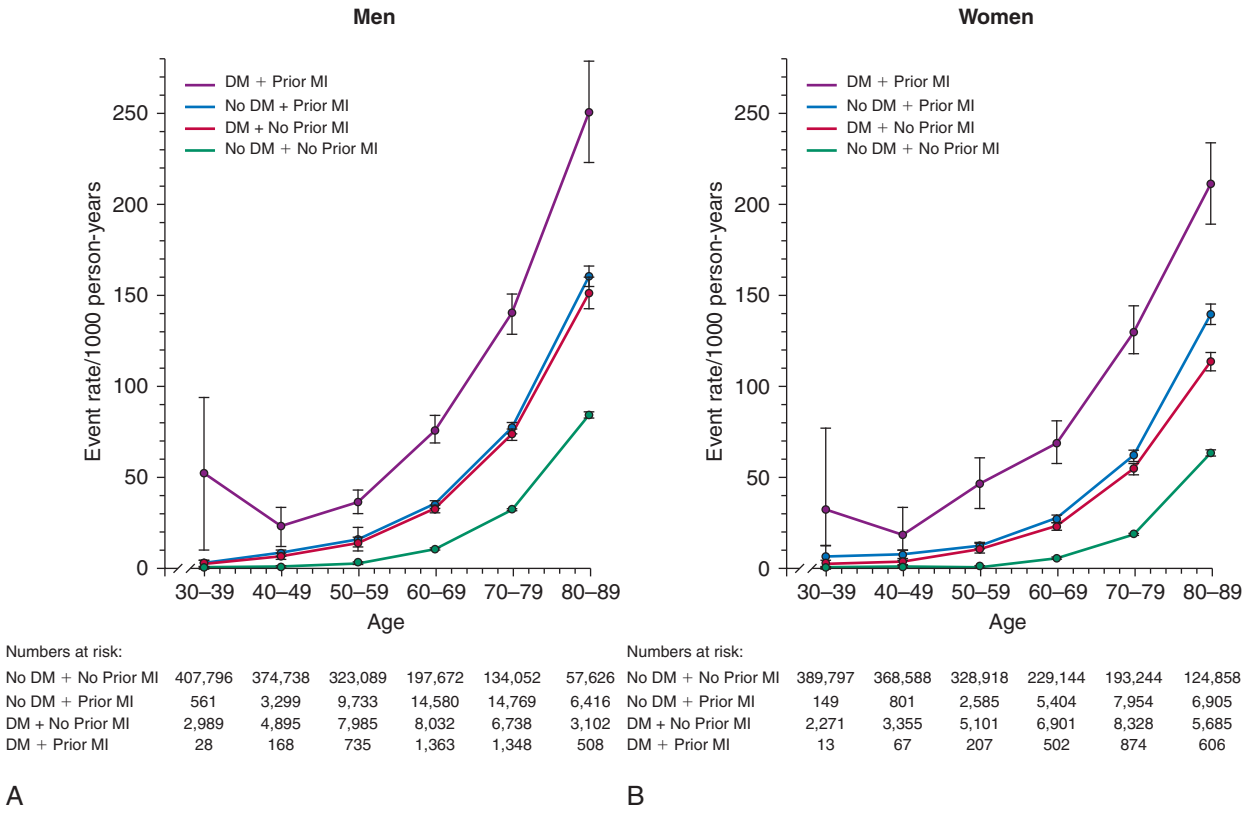


FIGURE 19-4 Event rates for cardiovascular mortality in men (A) and women (B) stratified by age in relation to diabetes mellitus (DM) and a prior myocardial infarction (MI). *(Modified from Schramm TK, Gislason GH, Køber L, et al: Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people,* Circulation *117:1945-1954, 2008.)*

TABLE 19-2 Events and Incidence Rates for Major Adverse Cardiovascular Complications Stratified by Diabetes Status and by Prior Myocardial Infarction

	EVENTS, N (%)*				
	NO DIABETES MELLITUS		DIABETES MELLITUS		
	No Prior MI	Prior MI	No Prior MI	Prior MI	Total
MI (Fatal or Nonfatal)					
Men	32,231 (2.2)	7,846 (15.9)	2,466 (7.3)	984 (23.7)	71,374 (2.2)
Women	21,787 (1.3)	3,325 (14.0)	2,168 (6.9)	587 (25.0)	
Stroke (Fatal or Nonfatal)					
Men	36,878 (2.5)	3,937 (7.8)	3,245 (9.6)	544 (27.4)	90,371 (2.8)
Women	40,535 (2.5)	2,152 (9.0)	3,118 (10.0)	322 (14.2)	
Coronary Death					
Men	24,135 (1.6)	8,226 (16.7)	2,511 (7.4)	1,137 (27.4)	67,816 (2.1)
Women	24,394 (1.5)	4,321 (18.2)	2,392 (7.6)	700 (30.9)	
Cardiovascular Death					
Men	51,698 (3.5)	9,928 (20.1)	4,937 (14.6)	1,417 (34.1)	139,985 (4.3)
Women	60,311 (3.7)	5,842 (24.5)	4,950 (15.6)	902 (39.8)	
MI or Coronary Death					
Men	44,579 (3.0)	12,461 (25.2)	3,735 (11.1)	1,583 (38.14)	108,882 (3.3)
Women	36,369 (2.2)	5,887 (24.7)	3,348 (10.6)	920 (40.5)	
MI, Stroke, or Cardiovascular Death					
Men	95,603 (6.4)	16,026 (32.5)	7,854 (23.3)	2,046 (49.3)	233,170 (7.1)
Women	94,922 (5.8)	8,190 (34.4)	7,332 (23.2)	1,197 (52.8)	
All-Cause Mortality					
Men	114,931 (7.7)	14,375 (29.1)	8,566 (25.4)	1,851 (44.6)	287,471 (8.8)
Women	129,844 (7.9)	8,393 (35.3)	8,365 (26.4)	1,146 (50.5)	

MI, Myocardial infarction.

*In percentages of the respective risk group (e.g., number of MIs in men with diabetes mellitus and prior MI and percentage of all men with diabetes mellitus and prior MI). Data from Schramm TK, Gislason GH, Køber L, et al: Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people, *Circulation* 117:1945-1954, 2008.

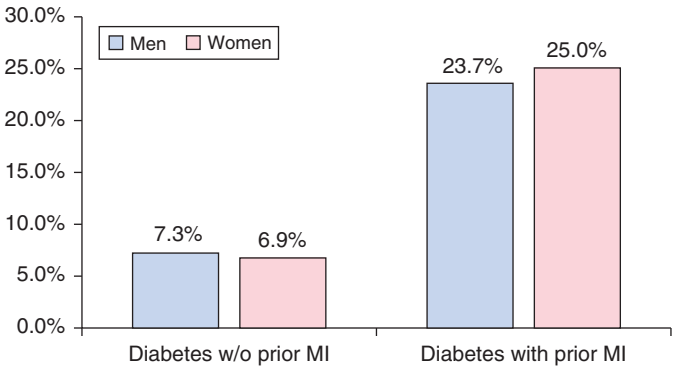


FIGURE 19-5 Incidence of myocardial infarction in patients with diabetes and with or without prior myocardial infarction for men and women during a 5-year follow-up. *(Modified from Schramm TK, Gislason GH, Køber L, et al: Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people,* Circulation *117:1945-1954, 2008.)*

DIABETES IN RANDOMIZED CONTROLLED TRIALS AND REGISTRY STUDIES OF ACUTE CORONARY SYNDROMES

RCTs are considered to provide the highest level of evidence for recommendations in scientific treatment guidelines. Ideally, they should be representative of the clinical population covered by the guideline recommendation. However, by nature, RCTs often exclude elderly patients and patients with certain comorbidities such as renal impairment and therefore lack generalizability of the study results to the real-world setting. For example, Steg and colleagues[7] compared patients with acute myocardial infarction enrolled in the Global Registry of Acute Coronary Events (GRACE) who had participated in a randomized trial, those who were trial eligible but who were not enrolled, and those who were ineligible. Patients who were enrolled in RCTs had a lower baseline risk and a lower mortality than patients who were not enrolled, even when they were trial eligible. Based on this analysis, the authors advised caution regarding extending the findings obtained in RCTs to the general population with acute myocardial infarction. In a review about the importance of translating data from randomized trials and registries into clinical information, Brown and colleagues[8] deplored that results of observational studies are often dismissed in favor of prospective randomized trials.

Prospective observational studies provide an unprecedented opportunity to at least estimate the epidemiology of diseases and the varying use of management strategies, as well as their outcomes, in consecutive patients in clinical practice. Data are gained from a "real-world" selection of patients, many of whom would be excluded from RCTs, in a variety of clinical settings. In RCTs of ACS, the number of patients with diabetes is generally lower than in observational studies of ACS. This may be because of older age and a higher prevalence of comorbidities such as renal impairment in patients with diabetes, which may lead to exclusion from RCTs. In 11 RCTs of the Thrombolysis in Myocardial Infarction (TIMI) Study Group evaluating ACS treatment,[9] only 17.1% of the study population had diabetes, as compared with 25% in the GRACE registry.[10] Surveys and registries also help to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop of performing clinical research, writing guidelines, and implementing the guidelines into clinical practice.[11] Observational studies form the basis of an important part of the medical knowledge we have today and are complementary to RCTs.[12] In the field of ACS, a plethora of national and international observational studies exist, such as GRACE,[13] the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative,[14] and the Euro Heart Survey ACS registry[15]; these studies describe the prevalence of diabetes and its impact on treatment patterns and outcomes in the real-world setting.

Diabetes in Randomized Controlled Trials of Acute Coronary Syndromes

Although entry criteria and objectives of RCTs have to be well defined to match the needs for future approval of new treatment strategies, those designing more recent RCTs have been trying to keep inclusion criteria as open as possible to better reflect the overall target patient population. Because of the high prevalence of diabetes in the population, less restrictive eligibility criteria, and larger trial sample sizes, the numbers and proportions of patients with diabetes enrolled into more recent RCTs has been reasonably high to allow reasonably powered analyses of the subsets of diabetes patients participating.

Donahoe and colleagues[9] analyzed the pooled data of 11 independent RCTs[16–26] of the TIMI Study Group, which evaluated ACS therapies in 62,036 patients (46,577 with ST-segment elevation myocardial infarction [STEMI] and 15,459 with non-ST-segment elevation acute coronary syndrome [NSTEMI-ACS]) from 1997 to 2006. The meta-analysis evaluated the influence of diabetes on mortality after an ACS. A total of 10,613 patients (17.1%) had prevalent diabetes at study entry. Patients with diabetes were older and more often had concomitant diseases as well as prior coronary interventions compared with those participants without diabetes (**Table 19-3**). After adjustment for differences in these baseline characteristics and the features of ACS management in the different trials, prevalent diabetes at presentation with ACS was independently associated with significantly higher 30-day and 1-year mortality rates for all ACS subsets, patients with STEMI, NSTEMI, and unstable angina (UA; **Table 19-4**).

Norhammar and colleagues[27] examined the associations between diabetes mellitus and outcomes in patients with ACS without ST-elevation even after consideration of the extent of coronary artery disease and revascularization strategies applied in the prospective, randomized multicenter FRISC II (Fragmin and Fast Revascularization During Instability of Coronary Artery Disease) randomized trial. This analysis comparing patients with and without diabetes randomized to primary invasive strategy versus not demonstrated that early revascularization of NSTE-ACS with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) seemed to have the same relative beneficial effect in both patients with and those without diabetes. However, the incidence of death and MI was significantly increased in patients with versus without diabetes in both treatment strategies, invasive and conservative (**Fig. 19-6**).

The proportion of patients with diabetes was even higher in the more recent Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction

TABLE 19-3 Baseline Characteristics of Patients With and Without Diabetes Presenting With Unstable Angina, Non-ST-elevation MI, or ST Elevation MI in 11 Independent Randomized Controlled Trials Evaluating ACS Therapy from 1997 to 2006

	ALL PATIENTS WITH ACS			PATIENTS WITH UA OR NSTEMI			PATIENTS WITH STEMI		
	With Diabetes (N=10,613)	Without Diabetes (N=51,423)	*P* Value	With Diabetes (N=3457)	Without Diabetes (N=12,002)	*P* Value	With Diabetes (N=7156)	Without Diabetes (N=39,421)	*P* Value
Age, median (IQR), yr	63 (55-71)	59 (51-69)	< 0.001	63 (55-70)	60 (52-69)	< 0.001	63 (55-71)	59 (50-68)	< 0.001
Age 75 yr or older (%)	(13.0)	(11.0)	< 0.001	(12.9)	(11.3)	< 0.001	(13.0)	(10.9)	< 0.001
Men No. (%)	7073 (66.6)	39,747 (77.3)	< 0.001	2220 (64.2)	8781 (73.2)	< 0.001	4853 (67.8)	30,966 (78.6)	< 0.001
Geographic region No. (%)									
North America	3504 (33.0)	12,808 (24.9)	< 0.001	2151 (62.2)	6595 (55.0)	< 0.001	1353 (18.9)	6212 (15.8)	< 0.001
Western Europe	2950 (27.8)	17,148 (33.4)	< 0.001	560 (16.2)	2859 (23.8)	< 0.001	2390 (33.4)	14,289 (36.3)	< 0.001
Other*	4159 (39.2)	21,467 (41.8)	< 0.001	746 (21.6)	2548 (21.2)	< 0.001	3413 (47.7)	18,919 (48.0)	< 0.001
BMI, median (IQR), kg/m^2	28.2 (25.4-31.5)	26.6 (24.2-29.4)	< 0.001	29.7 (26.6-33.3)	27.6 (25.0-30.7)	< 0.001	27.7 (25.0-30.9)	26.4 (24.2-29.3)	< 0.001
Current smoker, No./total No. (%)†	2970/10,590 (28.1)	23,630/51,321 (46.0)	< 0.001	734/3450 (21.3)	4228/11,979 (35.3)	< 0.001	2236/7140 (31.3)	19,402/39,342 (49.3)	< 0.001
History, No./total No. (%)									
Hypertension	6473/10,562 (61.3)	19,644/51,157 (38.4)	< 0.001	2449/3456 (70.9)	5819/12,001 (48.5)	< 0.001	4024/7106 (56.6)	13,825/39,156 (35.3)	< 0.001
Hyperlipidemia	2870/6872 (41.8)	8265/30,545 (27.1)	< 0.001	1538/2942 (52.3)	4059/9655 (42.0)	< 0.001	1332/3930 (33.9)	4206/20,890 (20.1)	< 0.001
Prior MI	2587/10,549 (24.5)	8386/51,267 (16.4)	< 0.001	1254/3453 (36.3)	3266/11,994 (27.2)	< 0.001	1333/7096 (18.8)	5120/39,273 (13.0)	< 0.001
Prior CABG surgery	853/10,612 (8.0)	2104/51,417 (4.1)	< 0.001	640/3457 (18.5)	1427/12,001 (11.9)	< 0.001	213/7155 (3.0)	677/39,416 (1.7)	< 0.001
Prior heart failture	754/10,558 (7.1)	1483/51,304 (2.9)	< 0.001	371/3452 (10.8)	548/11,996 (4.6)	< 0.001	383/7106 (5.4)	935/39,308 (2.4)	< 0.001
TIMI risk index, median (IQR)‡	21.8 (16.4-28.5)	18.9 (13.7-25.8)	< 0.001	21.2 (16.4-27.0)	19.2 (14.2-25.5)	< 0.001	22.2 (16.5-29.2)	18.8 (13.6-26.0)	< 0.001
Killip class 2-4 No./total No, (%)§	1191/8765 (13.6)	4362/45,362 (9.6)	< 0.001	209/2088 (10.0)	424/7413 (5.7)	< 0.001	982/6677 (14.7)	3938/37,949 (10.4)	< 0.001
Creatinine clearance, median (IQR), mL/min	83.0 (62.9-107.8)	84.7 (65.8-107.6)	< 0.001	90.4 (68.7-117.9)	90.5 (70.0-115.7)	< 0.001	79.8 (60.7-103.1)	83.2 (64.7-105.5)	< 0.001

SI conversion factor: To convert creatinine clearance to mL/sec, multiply by 0.0167.

BMI = Body mass index (calculated as weight in kilograms divided by height in meters squared); CABG = coronary artery bypass graft; IQR = interquartile range; NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

*Others includes Argentina, Australia, Belarus, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Estonia, Hong Kong, Hungary, India, Israel, Jordan, Korea, Latvia, Lebanon, Lithuania, Malaysia, New Zealand, Poland, Romania, Russia, South Africa, Singapore, Slovakia, Slovenia, Taiwan, Thailand, Turkey, Ukraine, Uruguay, and Venezuela.

†Current smokers are patients self-identified as currently smoking tobacco, irrespective of duration of smoking history or number of packs per day.

‡The range of scores for TIMI risk index for all patients with ACS are 3.3 to 107.5 for patients with diabetes and 1.6 to 131.2 for patients without diabetes; for patients with UA or NSTEMI, 4.0 to 80.8 with diabetes and 1.7 to 120.1 without diabetes; and for patients with STEMI, 3.3 to 107.5 with diabetes and 1.6 to 131.2 without diabetes.

§Killip class is a grading system of heart failure in the setting of ACS. Class I is defined as the absence of rales over the lung fields and the absence of an S_3; class II, the presence of rales that do not clear with coughing over one half or less of the lung fields or the presence of an S_3; class III, the presence of rales that do not clear with coughing over more than half the lung fields; and class IV, cardiogenic shock.

Data from Donahoe SM, Stewart GC, McCabe CH, et al: Diabetes and mortality following acute coronary syndromes, *JAMA* 298:765-775, 2007.

TABLE 19-4 Mortality at 30 Days and 1 Year of Patients With Versus Without Diabetes Presenting With Unstable Angina, Non-ST-segment Elevation MI, or ST-segment Elevation MI in 11 Independent Randomized Controlled Trials Evaluating Acute Coronary Syndrome Therapy from 1997 to 2006

	MORTALITY AT 30 DAYS			MORTALITY AT 1 YEAR*		
	INCIDENCE, %			INCIDENCE, %		
	With Diabetes	Without Diabetes	Adjusted OR (95% CI)†	With Diabetes	Without Diabetes	Adjusted OR (95% CI)‡
UA or NSTEMI	2.1	1.1	1.78 (1.24-2.56)	7.2	3.1	1.65 (1.30-2.10)
STEMI	8.5	5.4	1.40 (1.24-1.57)	13.2	8.1	1.22 (1.08-1.38)
All ACS	6.4	4.4	1.40 (1.26-1.56)	11.2	6.8	1.33 (1.20-1.48)

*Reported as Kaplan-Meier event rates at 12 months (360 days).
†Adjusted for age; sex; region of enrollment; smoking status; history of hypertension; prior myocardial infarction; congestive heart failure; coronary artery bypass graft surgery; systolic blood pressure; heart rate; creatinine clearance at enrollment; use of aspirin, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs); and hypolipidemic therapy during hospitalization for ACS. Infarct location and administration of thrombolytics were also included in the STEMI model.
‡Aspirin, beta blockers, ACE inhibitors or ARBs, thienopyridines, and lipid lowering therapy at time of discharge were included in the model.
Data from Donahoe SM, Stewart GC, McCabe CH, et al: Diabetes and mortality following acute coronary syndromes, *JAMA* 298:765-775, 2007.

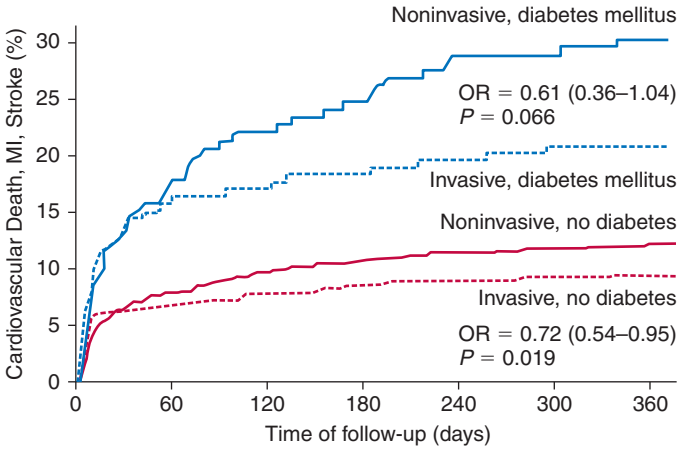


FIGURE 19-6 Outcome of patients with non-ST-segment elevation acute coronary syndromes with and without diabetes mellitus stratified by randomized treatment strategy (invasive versus noninvasive) in the FRISC II trial. *(Modified from Norhammar A, Malmberg K, Diderholm E, et al: Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization,* J Am Coll Cardiol *43:585-591, 2004.)*

(TRITON-TIMI 38) trial (23.1% with diabetes)[28] and the Study of Platelet Inhibition and Patient Outcomes (PLATO)[29] (25.0% with diabetes) comparing prasugrel and ticagrelor, respectively, with clopidogrel for the treatment of ACS. In both studies comparing different strategies of platelet inhibition in ACS, patients with versus without diabetes had significantly higher 1-year mortality (**Table 19-5**) independent of the treatment strategies (**Figs. 19-7** and **19-8**). (See also **Chapter 15**.)

Despite advances in the treatment of ACS on data from numerous RCTs, the magnitude of excess mortality associated with diabetes among patients with ACSs remains considerable, independent of the chosen treatment strata.

Diabetes in Registry Studies of Acute Coronary Syndromes

A range of prospective registries of patients with ACS are currently providing a wealth of standardized data regarding patient characteristics, clinical practices, and outcomes worldwide.

As part of the Euro Heart Survey Program of the European Society of Cardiology (ESC), several surveys and registries on treatment and outcome of ACS were undertaken from 2000 to 2008. The ACS I survey prospectively enrolled 10,484 patients across Europe in 2000 and 2001,[30] of whom 2352 (23.0%) had diabetes mellitus, 562 were treated with diet alone, 1112 received oral glucose lowering therapy alone, 561 were on insulin alone, and 117 received both oral and insulin treatment. The in-hospital mortality was significantly higher for patients with diabetes than for those without diabetes for STEMI (9.8% versus 5.7%), with an adjusted risk of in-hospital mortality of 1.6 (95% CI 1.2-2.1)[31]; insulin-treated patients had the worst mortality.

In the ACS II survey, conducted in 2004, 6385 patients with ACS were enrolled, of whom 1587 (25.0%) had prevalent diabetes.[32] In-hospital mortality was significantly higher in patients with diabetes for both STEMI (7.3% versus 4.6%) and NSTE-ACS (3.6% versus 1.9%).[33] Patients with diabetes had a significantly increased 1-year mortality after both STEMI and NSTE-ACS, with an even more pronounced difference in the latter patient group (**Fig. 19-9**). In a multivariable analysis adjusting for differences in baseline characteristics and in acute and long-term treatment, diabetes had an independent 37% increased odds for 1-year mortality (OR 1.37, 95% CI 1.09-.71).[33]

GRACE was a prospective observational study of patients hospitalized with ACS at 94 hospitals in 14 countries. In a subset of 16,116 patients hospitalized from April 1999 to September 2001, 25.0% had prevalent diabetes. Franklin and colleagues[10] reported that patients with diabetes were less likely to be treated according to guidelines and had an increased risk for heart failure, renal failure, cardiogenic shock, and death (**Table 19-6**).[10]

The CRUSADE quality improvement initiative compared adherence to treatment recommendations from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for NSTE-ACS among 46,410 patients from 413 U.S. hospitals. In this NSTE-ACS population, 33.1% of patients had prevalent diabetes.[34] Similar to the results from the GRACE registry,[10] patients with diabetes were less likely to receive guideline-recommended treatments. Hospital mortality was 5.4% in non–insulin-treated diabetes, 6.8% in patients with insulin-treated diabetes, and 4.4% in nondiabetic patients. The adjusted odds for death was 1.14 (95% CI 1.02-1.29) for non–insulin-treated diabetes and 1.29 (1.12-1.49) for insulin-treated diabetes as compared with patients without diabetes.[34] The odds for reinfarction as well as for congestive heart failure and red blood cell transfusion was similarly increased in the subset of patients with diabetes (**Table 19-7**).[34]

TABLE 19-5 Comparison of Patient Characteristics and Outcomes of Patients With and Without Diabetes in the TRITON and PLATO Trials

	TRITON TRIAL[29]			PLATO TRIAL[28]		
	Diabetes N = 3146 (23.1%)	No Diabetes N = 10,462 (76.9%)	*P*-Value	Diabetes N = 4662 (25.0%)	No Diabetes N= 13,951 (75.0%)	*P*-Value
Baseline Characteristics						
STEMI (%)	28.7	40.8	< 0.001	21.0	27.0	< 0.001
NSTE-ACS (%)	68.5	56.4	< 0.001	79	73	< 0.001
Age (yr)	63	60	< 0.001	64	61	< 0.001
Age older than 75 yr (%)	15.0	13.0	< 0.001	17.4	14.8	< 0.001
Women (%)	33.0	24.0	< 0.001	34.8	26.2	< 0.001
BMI (kg/m^2)	29.0	27.0	< 0.001	28.7	27.0	< 0.001
Hypertension (%)	80.0	59.0	< 0.001	81.6	60.1	< 0.001
Smoker (%)	27.0	41.0	< 0.001	24.8	39.6	< 0.001
Prior MI (%)	23.0	16.0	< 0.001	27.0	18.4	< 0.001
Prior CABG (%)	12.0	6.0	< 0.001	10.0	4.6	< 0.001
MI (%)	10.7	8.0	< 0.001	8.7	5.6	< 0.001
Composite Outcome Observed in the Trials						
CV death, MI, stroke (%)	14.6	9.9	< 0.001	15.2	9.3	< 0.001

CV = Cardiovascular.
Modified from Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the Trial to AssessImprovement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38, Circulation 2008;118:1626-36 and James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial, Euro Heart J 2010; 31:3006-3016.

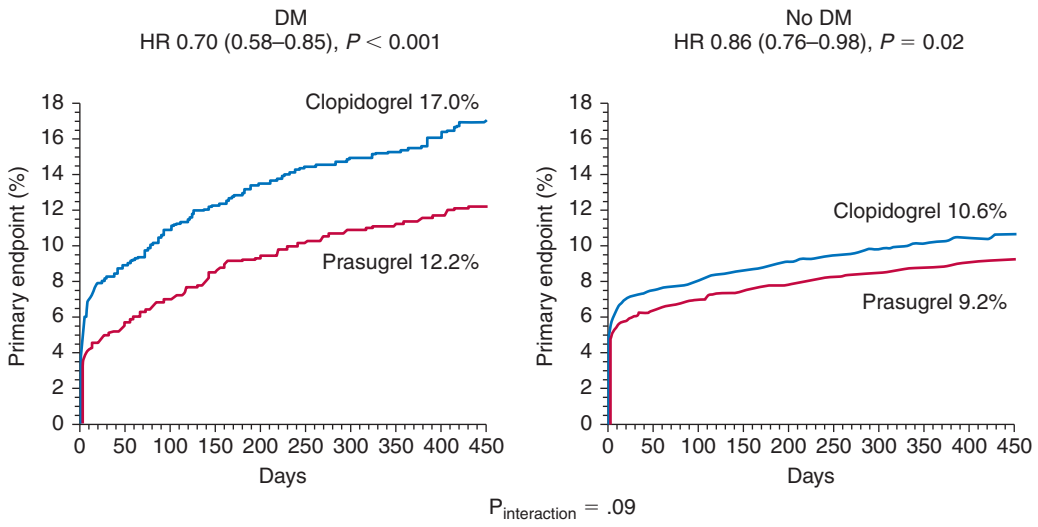


FIGURE 19-7 Kaplan-Meier curves for prasugrel versus clopidogrel stratified by diabetes status for the primary endpoint of death, nonfatal myocardial infarction, nonfatal stroke. *(Modified from Wiviott SD, Braunwald E, Angiolillo DJ, et al: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38,* Circulation *118:1626-1636, 2008.)*

All reported ACS registries come to the common conclusion that ACS patients with diabetes are less likely to receive guideline-recommended treatment and are more likely to experience short- and long-term adverse events.

The Euro Heart Survey on Diabetes and the Heart[35] recruited 3488 patients to study the prevalence of abnormal glucose regulation in adult patients with coronary artery disease, of whom two thirds presented with unstable coronary artery disease. Anselmino and colleagues[36] examined the impact of adherence to guidelines for medical treatment (evidence-based medication [EBM]) and for revascularization in patients with and without diabetes on long-term cardiovascular events (death, myocardial infarction, and stroke). Increased use of both EBM and revascularization was associated with lower event rates in patients with diabetes (11.6% versus 14.7% for EBM; 9.9% versus 16.9% for revascularization; **Fig. 19-10**). Although no separate analysis was provided to discriminate between patients with stable and unstable coronary artery disease, these data encourage the improved implementation of evidence-based guidelines to decrease adverse cardiovascular events, especially in patients with diabetes.

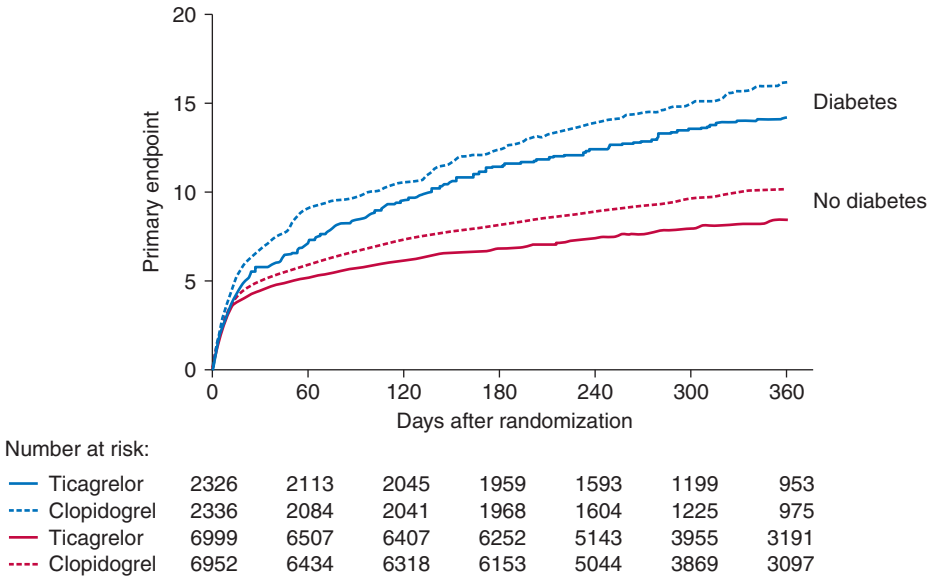


FIGURE 19-8 Kaplan-Meier curves for ticagrelor versus clopidogrel stratified by diabetes status for the primary endpoint of death, nonfatal myocardial infarction, nonfatal stroke. *(Modified from James S, Angiolillo DJ, Cornel JH, et al: Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial,* Eur Heart J *31:3006-3016, 2010.)*

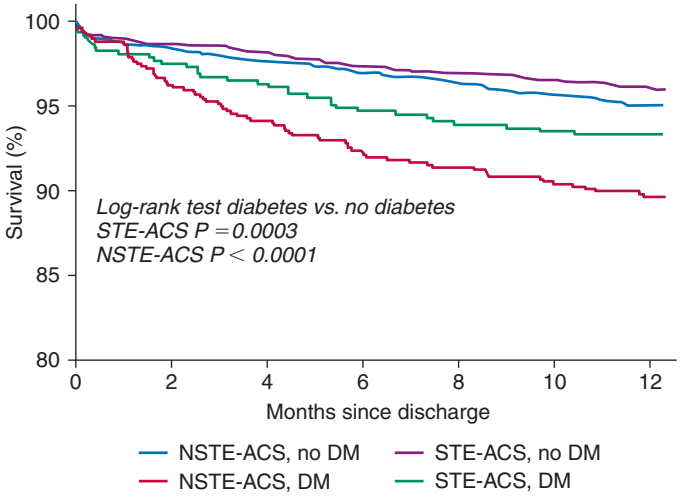


FIGURE 19-9 Kaplan–Meier curves for ST-segment elevation MI and non-ST-segment elevation acute coronary syndromes stratified by diabetes status for all-cause mortality during 1 year after hospitalization. The increase in mortality among patients with diabetes was even more pronounced in patients with non-ST-segment elevation acute coronary syndromes. *(Modified from Hasin T, Hochadel M, Gitt AK, et al: Comparison of treatment and outcome of acute coronary syndrome in patients with versus patients without diabetes mellitus,* Am J Cardiol *103:772-778, 2009.)*

UNDIAGNOSED DIABETES IN PATIENTS WITH CARDIOVASCULAR DISEASE AND ACUTE CORONARY SYNDROME EVENTS

Glucose intolerance and the associated traditional risk factors for cardiovascular disease, such as dyslipidemia and hypertension, might be present for many years before the diagnosis of diabetes mellitus is made.[37]

The Euro Heart Survey on Diabetes and the Heart[35] was undertaken to study the prevalence of abnormal glucose regulation in adult patients with coronary artery disease in Europe. A total of 4196 patients referred to a cardiologist because of CAD were enrolled, of whom 2107 were admitted on an acute basis (91% with ACS) and 2854 for elective consultation. Within the ACS population, 31.5% of patients had known diabetes mellitus. An oral glucose tolerance test (OGTT) was performed to characterize glucose metabolism in patients without previously known diabetes. In the 923 patients with ACS and without known diabetes, OGTT identified an additional 22% with newly diagnosed diabetes and a further 36% with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (**Fig. 19-11**). In addition to the patients with known diabetes in this population, most patients with ACS seen by cardiologists had pathologic

TABLE 19-6 The Association Between Diabetes Mellitus and Outcomes in Consecutive Patients With Acute Coronary Syndromes Participating in the GRACE-Registry

OUTCOME	STEMI*	NSTEMI*	UA*
Death	1.48 (1.03-2.13)	1.14 (0.85-1.52)	1.41 (1.02-1.95)
Cardiogenic shock	1.08 (0.76-1.53)	1.09 (0.79-1.50)	1.33 (0.88-2.02)
Heart failure	1.74 (1.43-2.11)	1.88 (1.60-2.21)	1.80 (1.50-2.18)
Renal failure	1.50 (1.00-2.23)	1.72 (1.32-2.25)	2.12 (1.45-3.08)

Comparison of patients with versus without diabetes for each endpoint.
NSTEMI = Non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.
*Data are adjusted odds ratio (95% confidence interval).
Data from Franklin K, Goldberg RJ, Spencer F, et al: Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events, *Arch Intern Med* 164:1457-1463; 2004.

TABLE 19-7 Clinical Outcomes in Patients With versus Without Diabetes Presenting With Non-ST-segment Elevation Acute Coronary Syndromes in the CRUSADE Registry

Clinical Outcome	No Diabetes	All Type 2 Diabetes	Insulin-Treated Diabetes	ADJUSTED ODDS RATIO (95% CI) All Type 2 Diabetes*	ADJUSTED ODDS RATIO (95% CI) Insulin-Treated Diabetes†
n	31,049	9,773	5,588		
Death (%)	4.4	5.4	6.8	1.14 (1.02-1.29)	1.29 (1.12-1.49)
Reinfarction (%)	3.2	3.5	3.8	1.07 (0.96-1.19)	1.07 (0.93-1.24)
Congestive heart failure (%)	8.0	12.4	13.7	1.25 (1.16-1.34)	1.19 (1.09-1.31)
Shock (%)	2.5	3.2	3.5	1.22 (1.05-1.41)	1.18 (0.97-1.44)
Red blood cell transfusion (%)	12.9	17.4	20.8	1.31 (1.23-1.40)	1.51 (1.40-1.63)

*No diabetes versus type 2 diabetes.
†No diabetes versus insulin-treated diabetes.
Data from Brogan GX Jr, Peterson ED, Mulgund J, et al: Treatment disparities in the care of patients with and without diabetes presenting with non-ST-segment elevation acute coronary syndromes, *Diabetes Care* 29:9-14, 2006.

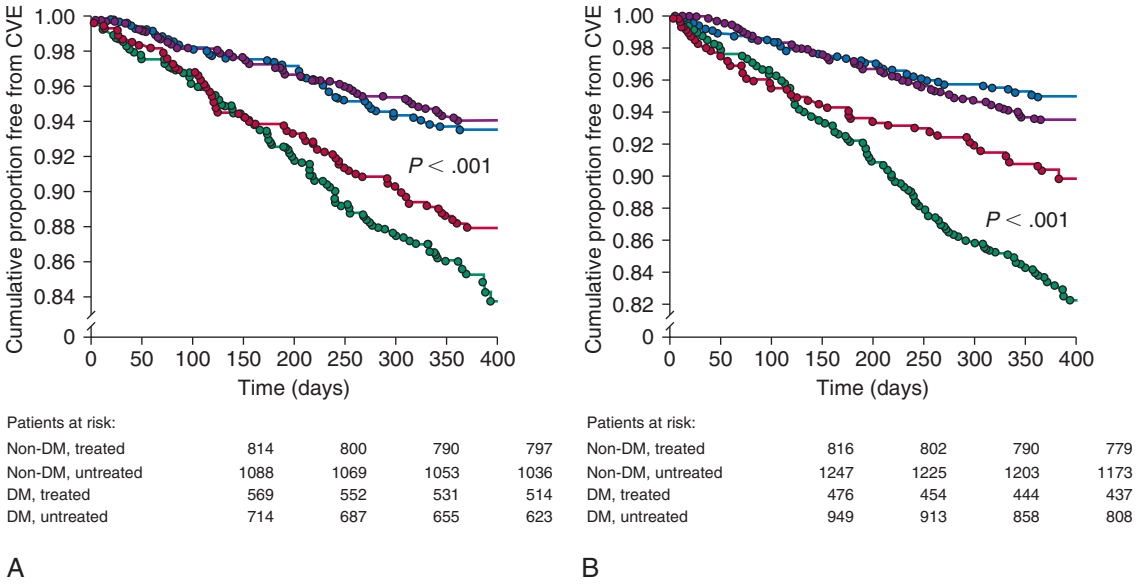


FIGURE 19-10 Kaplan-Meier curves cardiovascular events (CVE) comparing patients with and without DM who received evidence-based medicine (EBM, left panel) and who were revascularized or not (right panel). Non-DM without EBM / revascularization (blue circles), with EBM / revascularization (purple circles) and DM without EBM/ revascularization (green circles) with EBM / revascularization (red circles). CVE = Cardiovascular events. *(Modified from Anselmino M, Malmberg K, Ohrvik J, Rydén L; Euro Heart Survey Investigators: Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart,* Eur J Cardiovasc Prev Rehabil *15:216-23, 2008.)*

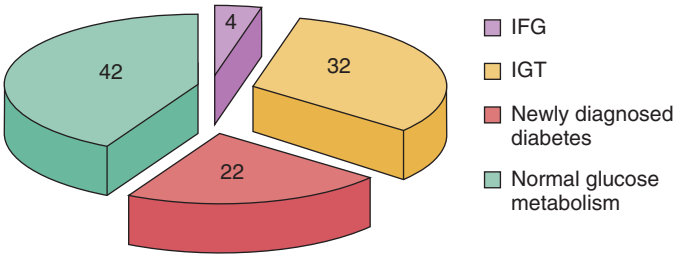


FIGURE 19-11 Glucose metabolism according to oral glucose tolerance tests in 923 patients admitted to the hospital for acute coronary syndromes without previously known diabetes. *(Modified from Bartnik M, Rydén L, Ferrari R, et al: The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart,* Eur Heart J *25:1880-1890, 2004.)*

glucose metabolism. The 1-year follow-up of this survey demonstrated that patients with newly diagnosed diabetes had a significantly higher mortality than patients with normal glucose metabolism (HR 2.0, 95% CI 1.1-3.6) (**Fig. 19-12**).[38]

The ESC and the European Association for the Study of Diabetes (EASD) published joint guidelines on the management of diabetes, prediabetes, and cardiovascular diseases.[39] Based on the findings of the Euro Heart Survey on Diabetes and the Heart,[35] it is recommended that screening for potential type 2 diabetes mellitus in patients with cardiovascular disease be initiated with hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) testing and that an OGTT be added if HbA1c and FPG are inconclusive.

The appropriateness of the routine performance of an OGTT to screen for diabetes during hospitalization for ACS has been controversial. Ye and colleagues[40] performed a meta-analysis of 15 prospective cohort studies assessing the accuracy and reproducibility of an OGTT in ACS (10 studies) and non-ACS (5 studies) patient populations. They reported that the OGTT in patients with ACS was as accurate as in non-ACS patients, and concluded that it was reasonable to screen patients hospitalized for ACS for otherwise undiagnosed diabetes mellitus using an OGTT.

A recently published subanalysis of the randomized Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial examined the prevalence of previously undiagnosed diabetes or

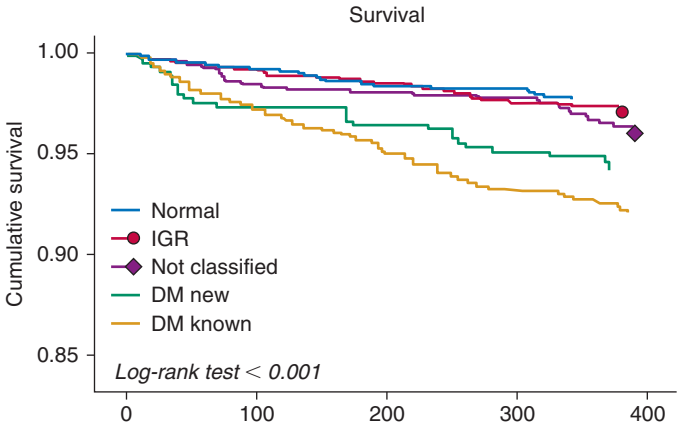


FIGURE 19-12 One-year outcome in relation to glycometabolic state in the Euro Heart Survey on Diabetes and the Heart of the European Society of Cardiology. Normal = normal glucose metabolism; DM known = previously known diabetes; DM new = newly diagnosed diabetes; IGR = impaired glucose regulation (impaired fasting glucose and/or impaired glucose tolerance); not classified = patients not classified, because no oral glucose tolerance test (OGTT) or fasting plasma glucose was performed. *(Modified from Lenzen M, Ryden L, Ohrvik J, et al: Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart,* Eur Heart J *27:2969-2974, 2006.)*

prediabetes and associations with ischemic outcomes among NSTE-ACS patients.[41] Patients were classified as having previously undiagnosed diabetes or prediabetes based on available data of FPG or HbA1c; no OGTT was performed in the trial. Of 8795 patients with available data of known diabetes or at least one of the reported glucose values, 2860 (32.5%) had known diabetes, 1069 (12.2%) were classified as having previously undiagnosed diabetes, and 947 (10.8%) were classified as having prediabetes. Both, patients with known diabetes and patients with previously undiagnosed diabetes had higher 30-day mortality (adjusted OR 1.40, 95% CI 1.01-1.93; and adjusted OR 1.65, 95% CI 1.09-2.48, respectively). Patients with prediabetes had similar

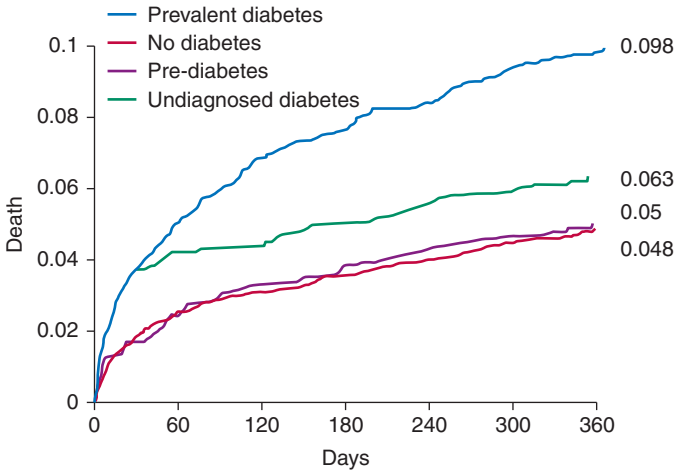


FIGURE 19-13 Unadjusted 1-year Kaplan-Meier mortality curves according to diabetes diagnosis group in patients with NSTE-ACS. Results of a subanalysis of the EARLY-ACS trial. Diagnosed = patients with known diabetes; no diabetes = patients with normal glucose metabolism; prediabetes = patients with fasting glucose greater than or equal to 110 and less than 126 mg/dL; undiagnosed = patients with previously undiagnosed diabetes, but fasting glucose greater than or equal to 126 mg/dL or HbA1c greater than or equal to 6.5% with no previous diabetes history. *(Modified from Giraldez RR, Clare RM, Lopes RD, et al: Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome,* Am Heart J *165:918-925.e2, 2013.)*

30-day death or MI outcomes as compared with patients with normal glucose metabolism. One-year mortality was higher for patients with known diabetes (adjusted HR 1.38, 95% CI 1.13-1.67) but not for patients with previously undiagnosed diabetes or prediabetes (**Fig. 19-13**).[41]

SUMMARY

Diabetes mellitus is a well-known risk factor for the development of cardiovascular diseases. The prevalence of diabetes will continue to grow worldwide, with about one-half of coronary artery disease patients with diabetes presently undiagnosed. Based on observational data, current guidelines therefore recommend screening for abnormal glucose metabolism in patients with coronary artery disease including those with ACS. This will be of clinical importance because both patients with known diabetes and those with newly diagnosed diabetes are less likely to receive evidence-based treatments and are more likely to develop cardiovascular adverse events. Reflecting the currently available epidemiologic data, diabetes will continue to have a strong impact on the incidence and outcomes of ACS in the future.

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20 Hyperglycemia and Acute Coronary Syndromes

Association with Outcomes and Management

Mikhail Kosiborod

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The observation that elevated glucose can occur in patients hospitalized with acute coronary syndromes (ACS; unstable angina, non–ST-segment elevation myocardial infarction [NSTEMI], and ST-segment elevation myocardial infarction [STEMI]) was made many decades ago.[1] Since then, numerous studies have documented that hyperglycemia is common, affects patients with and without established diabetes, and is associated with adverse outcomes, with a graded, incremental increase in the risk of mortality and complications observed across the spectrum of glucose elevations.[2–26] However, many gaps in knowledge remain. These include first and foremost the need for a better understanding of whether the glucose level is simply a risk marker of greater illness severity or a risk factor with a direct causal relationship to the adverse outcomes in patients with ACS. Furthermore, it remains unclear whether interventions to lower glucose in patients with ACS can improve patient outcomes, and if so, what the optimal targets, therapeutic strategies, and timing for such interventions should be during ACS events.

This chapter reviews what is presently known about the association between glucose levels and outcomes of patients hospitalized with ACS; describes the available data with regard to inpatient glucose management in this patient population, as well as comparative data across the spectrum of critically ill hospitalized patients; addresses the controversies in this field; and offers practical recommendations for patient management based on the existing data.

DEFINITION OF HYPERGLYCEMIA DURING ACUTE CORONARY SYNDROME

There is presently no uniform definition of what constitutes hyperglycemia in the setting of ACS. Prior studies used various blood glucose cut points ranging from 110 mg/dL or higher to 200 mg/dL or higher.[2] This uncertainty is compounded by variation in timing of glucose level assessments in this context. Most prior studies defined hyperglycemia based on the first available (admission or "on-arrival") glucose value,[2–11] whereas others used fasting glucose[12–17] as well as glucose values averaged over a period of time, such as the first 24 hours,[18–20] the first 48 hours, or the entire duration of hospitalization.[21] The American Heart Association (AHA) scientific statement on hyperglycemia and acute coronary syndrome suggests use of a random glucose level of above 140 mg/dL observed at any point over the course of hospitalization for ACS as the definition of hyperglycemia.[22] This recommendation is based in part on epidemiologic studies demonstrating that admission, mean 24-hour, 48-hour, and hospitalization glucose levels above approximately 120-140 mg/dL are associated with increased mortality risk,[7,18,19,21] and that decline in glucose levels below approximately 140 mg/dL during ACS hospitalization is associated with better survival,[23] although no cause-and-effect conclusions can be drawn from these data because of their observational nature.

It is important to note that the nature of the relationship between higher glucose levels and greater risk of mortality differs in patients with and without diabetes, with a paradoxically greater magnitude of association in those without versus those with prevalent diabetes.* The risk of mortality gradually rises when glucose levels exceed approximately 110-120 mg/dL in patients without diabetes, whereas in patients with established diabetes this risk does not increase significantly until glucose levels exceed approximately 200 mg/dL.[7,21] Thus, different thresholds may be appropriate to define hyperglycemia depending on the presence or absence of known diabetes.

PREVALENCE OF ELEVATED GLUCOSE LEVELS IN ACUTE CORONARY SYNDROME

Numerous studies have documented that elevated glucose levels occur commonly in patients hospitalized with ACS.[2–26] Although the definition of hyperglycemia varies across studies, the largest investigations show that the overall

*References 7, 9, 10, 12, 21, 23.

prevalence of elevated glucose levels (>140 mg/dL) at the time of hospital admission varies from 51% to 58%.[7,21] It is important to note that more than 50% of patients with ACS who have hyperglycemia on hospital arrival do not have known diabetes.[7]

Although glucose levels normalize in some ACS patients after admission (either spontaneously or as a result of targeted pharmacologic interventions),[24] persistent hyperglycemia remains present in more than 40% of patients throughout the course of hospitalization, and the prevalence of severe, sustained hyperglycemia (average hospitalization glucose >200 mg/dL) is approximately 14%.[21,25] Although persistent hyperglycemia occurs more commonly in patients with versus without established diabetes (78% versus 26%, respectively),[26] more than 40% of patients with persistent hyperglycemia do not have previously diagnosed diabetes.[21]

THE RELATIONSHIP BETWEEN GLUCOSE LEVELS AND MORTALITY IN ACUTE CORONARY SYNDROME

Multiple studies have now proven a powerful, independent relationship between elevated glucose and increased risk of mortality and other adverse clinical outcomes in patients hospitalized with ACS.[2–26] Plausible pathophysiologic underpinnings potentially contributing to these observed associations derive from a plethora of ex vivo, animal, and human studies that show that hyperglycemia may mediate adverse effects on inflammation, cell injury, apoptosis, ischemic myocardial metabolism, endothelial function, the coagulation cascade, and platelet aggregation in the setting of acute ischemia.[22,27] The association between higher glucose and greater mortality risk has been established across various glucose metrics[2–26,28] and across the spectrum of ACS[3] and applies to both short- and longer-term outcomes.[7,21]

The relationship between hyperglycemia and adverse outcomes among patients with ACS has been quantitatively summarized based on data from a large series of relatively small human studies collected over a period of three decades by Capes and colleagues.[2] This systematic overview demonstrated that among ACS patients without known diabetes, the relative risk of in-hospital mortality was 3.9 times higher in those with initial glucose 110 mg/dL or higher compared with normoglycemic patients (95% confidence interval [CI] 2.9-5.4). Among ACS patients with established diabetes, those with initial glucose of 180 mg/dL or higher had a 70% increase in the relative risk of in-hospital mortality, as compared with normoglycemic patients. More recent studies confirmed these findings and extended them across the broader range of ACS to include STEMI, NSTEMI, and unstable angina, demonstrating a significant increase in the risk of short- and long-term mortality, as well as incident heart failure in hyperglycemic ACS patients both with and without diabetes.[3,9,10] The largest observational study to date to address this issue used the data from Cooperative Cardiovascular Project and showed a near-linear relationship between higher admission glucose and greater risk of mortality at 30 days and at 1 year in more than 140,000 patients hospitalized with AMI.[7] A similar relationship between elevated glucose and increased risk of death was also shown with other glucose metrics, such as postadmission fasting glucose,[12,15–17] and with outcomes other than mortality, including such intermediates associated with adverse clinical outcomes as the "no-reflow phenomenon" following percutaneous coronary intervention (PCI)[29]; greater infarct size[7,21]; worse left ventricular systolic function[5]; and contrast-mediated acute kidney injury.[30,31]

The association between hyperglycemia and increased risk of death is not limited to the initial stages of ACS hospitalization. To the contrary, in a study of almost 17,000 patients hospitalized with acute myocardial infarction (AMI) in 40 U.S. hospitals, persistently elevated glucose during hospitalization was a better discriminator of adverse events than hyperglycemia on admission (C statistic 0.70 versus 0.62, $P < 0.0001$).[21] There was a significant, gradual increase in the risk of in-hospital mortality with rising mean hospitalization glucose levels (**Fig. 20-1**). Observational analyses from randomized clinical trials of glucose-insulin-potassium (GIK) therapy and of targeted glucose control in ACS also confirm the relationship between persistent hyperglycemia and increased mortality risk.[18,20]

Another important observation is that the nature of the relationship between higher glucose levels and increased mortality is different in patients with and without established diabetes.[7,21] Regardless of the glucose metrics used, the mortality risk starts rising at considerably lower glucose levels, and increases at a much steeper slope, in patients without previously diagnosed diabetes than in those with

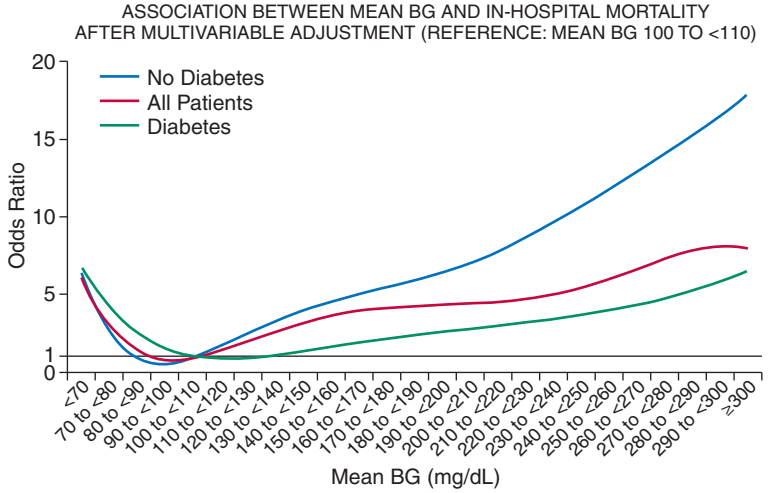


FIGURE 20-1 The association between average glucose values and risk of in-hospital mortality. BG = Blood glucose. *(Modified from Kosiborod M, Inzucchi SE, Krumholz HM, et al:* Circulation *117:1018-1027, 2008.)*

established diabetes (see **Fig. 20-1**). This phenomenon has been recently confirmed in other critically ill patient populations[32] and is not well understood. Several possible explanations have been proposed. Many patients with hyperglycemia in the absence of known diabetes actually have diabetes that simply was not recognized or treated before hospitalization,[33] representing a higher-risk cohort because other undiagnosed and untreated cardiovascular risk factors may be more prevalent in this group. Moreover, whereas the effect of targeted glucose control and insulin therapy in this clinical setting remains uncertain, nondiabetic ACS patients with hyperglycemia are less likely to be treated with insulin than those with established diabetes, even when glucose levels are markedly elevated.[7,28] Further contributing to this consistent observation is the fact that patients with established diabetes tend to have clustering of numerous risk factors that contribute to clinical risk, which may attenuate the magnitude of risk independently associated with any single factor, such as hyperglycemia. Finally, it is possible that higher degrees of stress and illness severity are required to produce similar degrees of hyperglycemia in patients without known diabetes compared with those with established diabetes.

DYNAMIC CHANGES IN GLUCOSE LEVELS DURING ACUTE CORONARY SYNDROME AND MORTALITY

Adding to the growing body of data on the relationship between hyperglycemia and adverse events in hospitalized ACS patients, several studies have shown that dynamic changes in glucose values are also strongly associated with patient survival. In post hoc analyses of data from the Complement and Reduction of Infarct Size after Angioplasty or Lytics (CARDINAL) trial, a randomized clinical trial that investigated the effect of a complement inhibitor, pexelizumab, in 1903 patients with STEMI, a decline in glucose of 30 mg/dL or more during the first 24 hours of hospitalization was associated with lower risk of 30-day mortality compared with the groups who had either no change or an increase in glucose values.[23] Similarly, in a study of approximately 8000 patients hospitalized with ACS in the United States who had hyperglycemia (glucose >140 mg/dL) on arrival, glucose normalization after admission was associated with better patient survival, even after adjustment for confounders (**Fig. 20-2**).[24] Whereas glucose normalization took place after insulin administration in some patients, many patients experienced normalization of their glucose values spontaneously (without any glucose-lowering interventions). It is interesting to note that improved survival was observed regardless of whether glucose normalization occurred as the result of insulin therapy or happened spontaneously. In fact, it was glucose normalization, and not insulin therapy per se, that was associated with better outcomes. These observational analyses highlight the uncertainty with regard to whether normalization of glucose levels during hospitalization simply identifies a lower-risk group of patients, reflects differences in patient care, or has a direct beneficial impact on survival.

CLINICAL TRIALS OF GLUCOSE CONTROL IN PATIENTS WITH ACUTE CORONARY SYNDROME

Although the strong relationship between elevated glucose levels and greater risk of death in patients with ACS is incontrovertible, one critical question remains unanswered: Is hyperglycemia a direct mediator of increased mortality and complications in patients with ACS, or is it simply a marker of greater disease severity and comorbidity? To definitively answer this question, large randomized clinical trials of target-driven intensive glucose control in hospitalized ACS patients are required. Because no such clinical outcomes trial has been performed to date, this issue continues to be highly controversial and cannot presently be addressed with certainty. Nevertheless, some insights may be gained from critical appraisal of the findings from small clinical trials of targeted glucose control in the ACS setting and trials of GIK therapy that used a hyperinsulinemic, hyperglycemic infusion strategy, as well as data from studies of targeted glucose control conducted in non-ACS clinical settings.

Because of marked variability in the insulin-infusion strategies used and the hypotheses tested across the clinical trials to date, one must first establish several key parameters to appropriately identify those randomized studies that

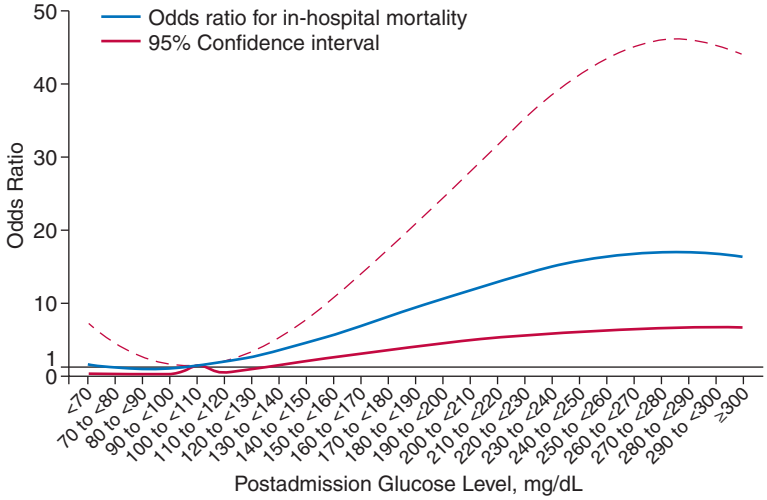


FIGURE 20-2 Glucose normalization and survival during hospitalization for acute myocardial infarction. *(Modified from Kosiborod M, Inzucchi SE, Krumholz HM, et al: Glucose normalization and outcomes in patients with acute myocardial infarction,* Arch Intern Med *169:438-446, 2009.)*

provide useful information with regard to the effect of targeted glucose control in the ACS setting. These parameters include the following:

- The presence of hyperglycemia at the time of patient randomization, with or without an antecedent diabetes diagnosis, because targeted glucose management is unlikely to yield benefit in the absence of hyperglycemia.
- Target-driven glucose control as the primary tested intervention, with substantially lower glucose targets in the intervention versus control arm.
- The achievement of a clinically and statistically significant difference in glucose values between intervention and control groups postrandomization.
- The assessment of treatment effects on meaningful patient outcomes, as opposed to intermediate endpoints.

To date, no ACS trial has fulfilled all of these criteria with any degree of rigor. A few studies fulfilling some but not all of these criteria are summarized in **Table 20-1**. The trial most closely satisfying the listed parameters is the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial, with a number of key caveats with regard to its interpretation.[34] In DIGAMI, patients presenting within 24 hours of acute MI symptoms with diabetes or initial glucose levels exceeding 198 mg/dL (11 mmol/L) were randomized to an acute and chronic insulin treatment regimen versus usual care. Those randomized to the insulin arm received 24 hours or more of intravenous (IV) dextrose-insulin infusion titrated to maintain glucose levels of 126 to 180 mg/dL, initiated at 5 units/hr of IV insulin in D_{5W}, followed by subcutaneous insulin injections three times daily for the subsequent 3 months titrated to standard therapeutic targets for glucose control, to be compared with usual care. The trial enrolled 620 patients, 80% of whom had previously diagnosed diabetes. Admission glucose at study entry was 277 mg/dL in the intervention group versus 283 mg/dL in the control group. By 24 hours, those randomized to the insulin arm had achieved significantly lower glucose levels compared with the control arm (173 versus 211 mg/dL; $P<0.0001$), although average glucose values remained significantly elevated in both groups; the differences between the groups were smaller by hospital discharge but remained statistically significant (148 versus 162 mg/dL; $P<0.01$). Despite this early contrast in glucose levels between the groups, no significant differences in fasting glucose values were observed at any subsequent timepoint throughout the follow-up extending over 12 months from enrollment; however, hemoglobin A1c (HbA1c) levels were significantly lower in the intervention versus control group at 3 months (7.0 versus 7.5%, $P<0.01$). Also of note, hypoglycemia (not explicitly defined in the initial study reports) was observed in 15% of the insulin infusion patients compared with none in the usual care group, and in 10% of participants resulted in discontinuation of the protocol treatment. For the primary endpoint of all-cause mortality at 3 months, there was no significant difference between the randomized groups (38 versus 49 deaths), with the respective P value reported as "not significant".[34] Therefore, from a "purist" perspective, based on failure to achieve statistical significance in the primary endpoint, DIGAMI was a negative trial. However, subsequent analyses of mortality at both 1 year and 3.5 years of follow-up showed clinically and statistically significant reductions in all-cause mortality in the insulin-treated group versus control (at 1 year: 18.6% versus 26.1%, $P=0.027$; at 3.5 years: 33% versus 44%, $P=0.011$, respectively).[34,35] If one accepts the validity of the mortality reduction observed in the longer-term analyses, the relative contributions of the various aspects of the trial remain uncertain, including the effects of the acute dextrose-insulin infusion and the effects of multidose insulin injection in the outpatient setting. Therefore, although the DIGAMI data are the most compelling in the field of targeted glucose control for the treatment of ACS, the relative attribution of improved survival to acute, in-hospital glucose lowering remains uncertain.

Beyond DIGAMI, a few other studies satisfy some (but not all) of the proposed parameters of validity and generalizability with regard to targeted glycemic control in the ACS setting. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) trial was designed to assess the effect of dextrose-insulin infusion versus usual care in patients with MI and hyperglycemia on arrival. Similar to DIGAMI, the therapeutic target for the insulin arm was 72 to 180 mg/dL, and IV dextrose was infused with the insulin (either D_{5W} or D_{10W}); however, the insulin dose was much lower in HI-5 at 2 units/hr (contrasted with 5 units/hr used both in DIGAMI and in most trials of GIK therapy).[36] The HI-5 trial was terminated early because of slow enrollment and failed to achieve a statistically significant difference in glucose values between the intensive and conventional glucose groups (149 versus 162 mg/dL 24 hours postrandomization, $P=$NS).[18] Mortality assessments at hospital discharge, 30 days, and 6 months all numerically favored usual care over targeted glucose control with insulin treatment, although none of these comparisons were statistically significant because of very low numbers of events (6 months: 10 versus 7 deaths; $P=0.62$).

The DIGAMI-2 multicenter study attempted to determine whether potential survival benefit seen with targeted glucose control in the original DIGAMI study was primarily attributable to acute or chronic glucose lowering with insulin.[37] In DIGAMI-2, 1253 patients with acute MI and diabetes or admission glucose above 198 mg/dL were randomized to one of the three subgroups: (1) 24-hour insulin-glucose infusion targeting glucose of 126 to 180 mg/dL, followed by a subcutaneous insulin-based long-term glucose control regimen (group 1, identical to the original DIGAMI intervention group); (2) same 24-hour insulin-glucose infusion, but followed by standard glucose control (group 2); and (3) routine glucose management (group 3). Of note, the trial planned to recruit 3000 patients and was stopped prematurely because of slow recruitment. Glucose levels on arrival were similar among the three arms (approximately 229 mg/dL). At 24 hours postrandomization the glucose levels were modestly lower in the two groups assigned to acute glucose lowering versus control (164 versus 180 mg/dL, $P<0.01$). This difference, although statistically significant, was clinically small and considerably less than expected; it was also much smaller than what was observed in the original DIGAMI study. There was no difference in either glucose or HbA1c levels among the three groups at any other timepoint, with up to 3 years of follow up. It is important to note that patients in group 1 failed to achieve the targeted fasting glucose range of 90 to 126 mg/dL during the outpatient management phase. Mortality over 2 years was not statistically different among the three groups (23.4% versus 21.2% and 17.9% in groups 1, 2, and 3, respectively; $P=0.83$ for group 1 versus group 2, and $P=0.16$ for group 1 versus group 3). Because of its limitations (primarily lack of substantial contrast in glucose levels among the three

TABLE 20-1 Clinical Trials of Glucose Control in Acute Coronary Syndrome*

TRIAL	TARGETED GLUCOSE CONTROL	ELEVATED BG ON ENTRY	GLUCOSE TARGETS SPECIFIED	BG CONTRAST ACHIEVED	CLINICAL ENDPOINTS	RESULTS
DIGAMI (1995)	+/–	+ Approximately 280 mg/dL	+ 126-180 mg/dL versus usual care acutely, 90-126 mg/dL fasting BG versus usual care afterward	+/– 173 versus 211 mg/dL during first 24 hr; difference in HbA1c but not fasting BG afterward	+	+/– Mortality neutral at 3 months (primary endpoint), improved survival in glucose control arm by 1 year
DIGAMI-2 (2005)	+/–	+ 229 mg/dL	+ 126-180 mg/dL in-hospital versus usual care acutely, 90-126 mg/dL fasting BG (group 1 only) versus usual care afterward	+/– 164 versus 180 mg/dL at 24 hr, no difference afterward	+	– Mortality neutral among three groups
HI-5 (2006)	+/–	+ Approximately 198 mg/dL	+ 72-180 mg/dL versus usual care	– 149 versus 162 mg/dL (P=NS) during first 24 hr	+	– Mortality neutral in hospital, at 3 and 6 months
Marfella et al (2009)	+	+ ≥140 mg/dL	+ 80-140 versus 180-200 mg/dL	+ 163 versus 192 mg/dL	–	+/– Higher ejection fraction, less oxidative stress, less inflammation and apoptosis in the intensive versus standard group
Marfella et al (2012)	+	+ ≥140 mg/dL	+ 80-140 versus 180-200 mg/dL or GIK	+ 161 versus 194 versus 182 mg/dL	–	+/– More regenerative potential in the peri-infarcted areas in the intensive versus conventional and GIK groups
Marfella et al (2013, myocardial salvage)	+	+ ≥140 mg/dL	+ 80-140 versus 180-200 mg/dL	+ 144 versus 201 mg/dL	–	+/– Greater myocardial salvage in the intensive versus standard group
Marfella et al (2013, ISR)	+	+ ≥140 mg/dL	+ 80-140 versus 180-200 mg/dL	+ 145 versus 191 mg/dL	–	+/– Lower ISR in the intensive versus standard group
RECREATE pilot (2012)	+	+ ≥144 mg/dL	+ 90-117 mg/dL versus usual care	+ 117 versus 143 mg/dL	–	+/– Significant difference in glucose between intensive and standard groups (primary endpoint) No difference in mortality (small number of events)
BIOMArCS-2 (2013)	+	+ ≥140 mg/dL	+ 85-110 mg/dL during day, 85-139 mg/dL at night versus <288 mg/dL	+ 112 mg/dL versus approximately 130 mg/dL	+	– No difference in infarct size by high-sensitive troponin; composite of in-hospital death and reinfarction higher in the intensive versus standard group (very small number of events)

*Full clinical trials names represented by acronyms are as follows:
- DIGAMI—Diabetes Insulin-Glucose in Acute Myocardial Infarction
- HI-5—Hyperglycemia: Intensive Insulin Infusion in Infarction
- RECREATE—Researching Coronary Reduction by Appropriately Targeting Euglycemia
- BIOMArCS-2—Biomarker Study to Identify the Acute Risk of a Coronary Syndrome 2

+=Yes, –=No.
BG=Blood glucose; GIK=glucose-insulin-potassium; ISR=in-stent restenosis.

groups), the DIGAMI-2 study did not provide a definitive answer on whether targeted glucose lowering (whether acute or chronic) has any clinical value in patients with AMI.

Several additional, smaller randomized clinical trials of intensive versus conventional glucose control in AMI have primarily tested mechanistic hypotheses, as well as the effectiveness of streamlined insulin infusion protocol in lowering glucose compared with usual care, and feasibility of its implementation internationally (including in resource-limited areas).[27,38–41] Marfella and colleagues randomized 50 patients with AMI and hyperglycemia (admission blood glucose [BG] ≥140 mg/dL) who had coronary angiography

and were subsequently referred for coronary bypass surgery to either intensive or conventional glucose control for 3 days preoperatively; AMI patients requiring coronary artery bypass grafting (CABG) who had normal admission glucose levels served as controls.[27] Two-dimensional echocardiography was performed on patient admission and after achievement of glucose treatment goals. All patients underwent myocardial biopsy of peri-infarcted areas; specimens were subjected to a variety of immunohistochemical and biochemical analyses. Patients in the intensive treatment group achieved greater reduction in glucose values (78 versus 10 mg/dL reductions), but also had higher hypoglycemia rates. Compared with the conventional treatment group, patients in the intensive group had higher ejection fraction, less oxidative stress, and less inflammation and apoptosis in peri-infarcted specimens. However, the study was too small for clinically meaningful outcomes to be evaluated.

The same group subsequently embarked on an additional small randomized trial with almost identical design, except that patients could be randomized to three different arms: intensive glucose control, conventional control, or GIK.[39] Patients in the intensive control group exhibited more regenerative potential (as analyzed by myocyte precursor cells) in the peri-infarcted areas than those in the conventional and GIK groups. Two subsequent randomized trials by the same investigators evaluated the effect of intensive glucose control (versus conventional management) on myocardial salvage index among 106 hyperglycemic patients with STEMI undergoing PCI[38]; and on in-stent restenosis in 165 hyperglycemic patients with STEMI undergoing PCI.[40] Despite relatively small sample sizes, both studies showed clinically and statistically significant benefits of intensive versus conventional periprocedural glucose control in terms of both greater myocardial salvage (15% versus 7%, $P<0.05$) and lower rates of in-stent restenosis at 6 months (24% versus 46%, $P<0.05$). These clinical trials, although elegant, well conducted, and intriguing in their findings, require confirmation in larger studies before their results can be extrapolated to routine clinical care.

The International Multicentre Randomized Controlled Trial of Intensive Insulin Therapy Targeting Normoglycemia In Acute Myocardial Infarction: RECREATE (Researching Coronary Reduction by Appropriately Targeting Euglycemia) was a randomized open-label pilot study of targeted glucose control in patients with STEMI, with the main objective of testing the feasibility and safety of implementing a streamlined glucose control protocol across international sites, many in resource-limited environments.[41] A total of 287 patients with STEMI and initial glucose values equal to or above 144 mg/dL were randomly assigned to either intensive glucose control with a streamlined IV insulin infusion protocol or usual care. Patients in the intensive arm were treated with IV infusion of insulin glulisine for at least 24 hours and for as long as critical care unit (CCU)–level care was required, with a target glucose range of 90-117 mg/dL. Once transferred to the ward, patients in the intensive arm were switched to insulin glargine and continued this treatment for a total duration of 30 days postrandomization. Patients in the control arm received usual care for AMI, according to local practice of each participating center. Because RECREATE was a pilot study designed to demonstrate the feasibility of targeted glucose control in STEMI with a simplified insulin infusion protocol, the primary endpoint was 24-hour difference in mean glucose between the two study groups. At 24 hours, mean glucose was significantly lower in the intervention arm versus the standard care arm (117 versus 143 mg/dL); however, at 30 days HbA1c was similar between the groups. Although the overall rates of hypoglycemia (<70 mg/dL) were significantly higher in the intensive versus the standard group (22.7 versus 4.4%, $P<0.05$), there was only one episode of severe hypoglycemia (<50 mg/dL). The rates of mortality at 90 days were not different in the intensive versus the standard group (12 versus 13 events); however, the study lacked statistical power to provide definitive answers with regard to clinical outcomes. The RECREATE pilot demonstrated that paper-based glucose control protocols can be effectively implemented across multiple centers, including those in resource-limited environments, with very low rates of severe hypoglycemia. However, given its limited sample size, it did not address the question of whether better glucose control can reduce adverse events in patients with AMI.

The most recent study of glucose control in AMI was the randomized Biomarker Study to Identify the Acute Risk of a Coronary Syndrome 2 (BIOMArCS-2).[42] BIOMArCS-2 was a prospective, single-center, open-label clinical trial that randomized 294 patients with ACS (280 patients in the final analytic dataset; 82% with STEMI) and admission glucose level from 140 to 288 mg/dL to either intensive glucose control for 48 hours (target glucose of 85 to 110 mg/dL during the day; 85 to 139 mg/dL at night) or conventional management (target glucose <288 mg/dL). Primary outcome measure was high-sensitivity troponin T value 72 hours postadmission (hsTropT72, as a marker of infarct size). The extent of myocardial injury was also measured at 6 weeks with myocardial perfusion scintigraphy (myocardial perfusion imaging using single photon emission computed tomography [MPI-SPECT]). Glucose values were significantly lower in the intensive versus the conventional group at 6, 12, 24, and 36 hours, and equalized by 72 hours. Severe hypoglycemia (<50 mg/dL) occurred in 13 patients (9%) randomized to the intensive glucose control group. There was no significant difference in hsTropT72 between the groups (1197 versus 1354 ng/L, $P=0.41$). The median extent of myocardial injury as revealed by MPI-SPECT was numerically lower in the intensive versus the conventional group, but this difference did not reach statistical significance (2% versus 4% respectively, $P=0.07$). The number of in-hospital deaths and recurrent MIs was very small (nine events in total), but these events occurred more frequently in the intensive versus the conventional group (eight events versus one event, respectively, $P=0.04$). The results of the BIOMArCS-2 study suggest that intensive glucose control after AMI does not reduce infarct size as measured by high-sensitivity troponin essay, but increases the risk of hypoglycemia and, possibly, composite of in-hospital death and recurrent MI. However, given that the number of events in the study was very small; that it had a single-center and open-label design; that the findings conflict with those of other small clinical trials that showed reduction in infarct size with intensive versus conventional glucose control[38]; and that no difference in mortality was found between the groups (despite the higher number of events in the intervention arm),[41] the results of BIOMArCS-2 are difficult to interpret.

The remaining trials evaluating the effects of insulin infusion on clinical outcomes in the ACS setting have



TABLE 20-2 Clinical Trials of Glucose-Insulin-Potassium (GIK) Therapy in Acute Coronary Syndrome*

TRIAL	TARGETED GLUCOSE CONTROL	ELEVATED BG ON ENTRY	GLUCOSE TARGETS SPECIFIED	BG CONTRAST ACHIEVED	CLINICAL ENDPOINTS	RESULTS
Pol-GIK (1999)	–	– 124 mg/dL	–	N/A 106 versus 112 mg/dL in intervention versus control arms	+	Significantly higher mortality in intervention versus control arm at 35 days
CREATE-ECLA (2005)	–	+ 162 mg/dL	–	N/A Glucose higher in intervention arm versus control (187 versus 148 mg/dL)	+	Mortality neutral
IMMEDIATE (2012)	–	Not specified	–	N/A	+	No difference in progression to AMI, 30-day mortality, or HF. Composite of in-hospital mortality or cardiac arrest lower in the GIK versus placebo group

*Full clinical trials names represented by acronyms are as follows:
- Pol-GIK—Poland Glucose-Insulin-Potassium trial
- CREATE-ECLA—Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation—Estudios Cardiológicos Latinoamérica
- IMMEDIATE—Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care

+ = Yes, – = No.
AMI = Acute myocardial infarction; BG = blood glucose; HF = heart failure.

predominantly tested the GIK hypothesis (i.e., hyperinsulinemic, hyperglycemic therapy), as summarized in published quantitative analyses,[43] and have little to do with target-driven glucose control (**Table 20-2**). Studies such as the Glucose-Insulin-Potassium (GIPS) trial[44] or the much larger Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation—Estudios Cardiológicos Latinoamérica (CREATE-ECLA) and the Organization to Assess Strategies for Ischemic Syndromes (OASIS) 6 trials (which in total randomized almost 23,000 participants)[19] assigned patients to fixed-dose GIK infusion regardless of their initial glucose values or diabetes status, and did not prespecify targets for glucose control. In these studies, as dictated by the infusion protocols, high-dose delivery of insulin was supported by IV glucose administration to affect modest hyperglycemia, defined by protocol as a range of 126 to 198 mg/dL. For example, in the CREATE-ECLA trial, which enrolled more than 20,000 patients with acute MI and demonstrated no discernible treatment benefit with GIK therapy,[19] 6-hour postrandomization glucose values were significantly higher in the GIK group than in the control group (187 versus 148 mg/dL). Thus, the GIK studies were not designed to evaluate targeted glucose control with insulin, and their findings should not be used in guiding decisions about glucose management in ACS.

The Poland Glucose-Insulin-Potassium (Pol-GIK) trial randomized 954 patients with acute MI to either to fixed low-dose GIK, which included a much lower rate of insulin infusion (0.8 to 1.3 units/hr) than typical GIK regimens, versus normal saline infusion.[45] Although not a typical GIK trial, insofar as it used a much lower insulin dose, Pol-GIK cannot be considered a study of targeted glucose control either. First, it randomized patients who were on average normoglycemic at study entry (initial glucose level of approximately 124 mg/dL in both groups). It is therefore not entirely surprising that excess hypoglycemia was observed in the intervention arm, which required lowering of the fixed insulin dose during the conducting of the trial from 1.3 to 0.8 units/hour. Second, and similar to other GIK studies, no glucose goals were prespecified or aimed for in this study and the dose of GIK infusion was fixed and not adjusted to maintain a certain range of glucose values. As a result, there was no significant difference in glucose levels 24 hours postrandomization (106 mg/dL in GIK versus 112 mg/dL in the control arm). The study was stopped prematurely because of excess mortality in the GIK arm at 35 days (8.9% versus 4.8% in the control arm, $P = 0.01$). However, as a result of the serious limitations of interpretation stemming from the intent of the trial to evaluate the effect of fixed-dose administration of insulin rather than a targeted glucose control hypothesis, no valuable lessons can be learned about glucose lowering and patient outcomes in AMI based on its results.

The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial was a National Institutes of Health–sponsored randomized, placebo-controlled, double-blinded, multicenter clinical trial of GIK infusion (1.5 ml/kg/hr, continuous infusion for a total of 12 hours) versus matching placebo administered as early as possible in the setting of suspected ACS in the prehospital emergency medical service (EMS) setting. The IMMEDIATE trial was specifically designed to test the GIK hypothesis and was not a study of targeted glucose control in ACS. Similar to previous GIK trials, the presence of hyperglycemia was not required as an inclusion criterion, and there were no prespecified goals for glucose control. The primary hypothesis was that early GIK administration would prevent progression of suspected ACS to AMI within 24 hours, as determined by biomarker and electrocardiographic evidence of myocardial necrosis. Major secondary hypotheses were that GIK infusion would reduce mortality (at 30 days and 1 year), reduce prehospital or in-hospital cardiac arrest and in-hospital mortality, and reduce hospitalizations for heart failure. A small biologic cohort substudy also evaluated the impact of GIK infusion on infarct size.

A total of 871 patients (411 in the GIK group, 460 in the placebo group) were evaluated in the final analysis. There was no significant difference between the GIK and placebo groups in progression to AMI (48.7 versus 52.6%, $P = 0.28$), 30-day mortality (4.4 versus 6.1%, $P = 0.27$), or 30-day heart failure (1.5 versus 2.2%, $P = 0.43$).[46] The rates of prespecified composite of cardiac arrest or in-hospital mortality were significantly lower in the GIK group (4.4 versus 8.7%, $P = 0.01$); however, evaluation of secondary endpoints did not include

statistical adjustment for multiple comparisons. The results were similar when tested among patients with STEMI. In a small biologic mechanism cohort (110 patients in total), GIK significantly reduced infarct size compared with placebo (2% versus 10% of left ventricular [LV] mass, respectively; $P=0.01$), and significantly reduced the level of free fatty acids. Although the results from this small substudy of IMMEDIATE are intriguing, they are hypothesis generating only, and would need to be tested in a larger randomized clinical trial. Overall, the results of IMMEDIATE showed no significant clinical benefit of early GIK administration in patients with suspected ACS.

In summary, no definitive clinical trial of targeted glucose control in ACS has been performed, and the data from the existing small studies are conflicting and inconclusive. In this context, one might be tempted to look for more definitive answers in the broader critical care field of patients in other clinical settings. In 2001, van den Berghe and colleagues reported marked beneficial effects associated with normalization of blood glucose through use of an insulin infusion compared with usual care among patients hospitalized in a surgical intensive care unit (SICU).[47] These observations fueled enthusiasm among clinicians and professional societies to endorse a strategy of targeted glucose control across critically ill hospitalized populations.[48] However, in the 8 years that followed, several additional randomized trials in various ICU patient populations failed to reproduce these beneficial results.[49–53] Key among these more recent trials include the same investigators at the same institution, using the same protocol as in the SICU trial, testing intensive glucose lowering in medical intensive care unit (ICU) patients, and demonstrating lower morbidity, but no difference in the trial primary endpoint of mortality with intensive glucose lowering versus usual care.[53] In addition, the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which was the largest trial of targeted glucose control in critically ill patients across ICU settings, demonstrated significantly higher mortality with intensive versus more conservative glucose control.[50] These results have substantially tempered enthusiasm for aggressive glucose lowering in the ICU setting. However, the results of NICE-SUGAR need to be interpreted in the context of the study design; NICE-SUGAR compared "very intensive" glucose control to "good" glucose control, not to "usual care." Specifically, an IV insulin protocol was used in more than two thirds of patients in the control arm, producing an average glucose level of approximately 142 mg/dL. This degree of glucose control is more intensive than what was achieved in control groups of other critical care studies, lower than what was achieved in the intensive arm of many ACS studies, and much lower than what is typically seen in routine clinical care. Thus the most appropriate conclusion from the NICE-SUGAR study is that "moderate" glucose control (with values ranging from 140 to 180 mg/dL) is sufficient, and more aggressive glucose lowering provides no additive benefit, and may even be harmful.

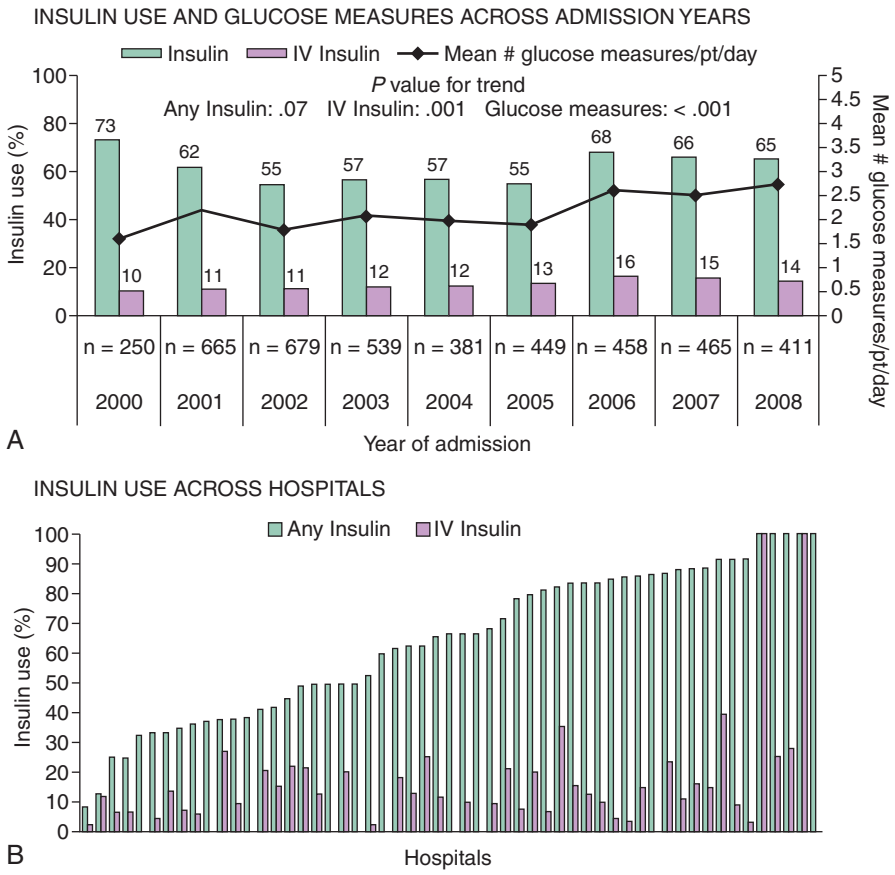
Regardless, extrapolation of observations from trials outside the ACS setting is problematic. Specifically, the findings from patients hospitalized with surgical illness, trauma, and sepsis cannot be simply extended to those with ACS. The pathophysiology of these conditions is different, and the treatment thresholds and targets may be distinct as well. Prior studies have shown that the relationship between glucose values and mortality may vary significantly across various cardiovascular conditions[7,54]; thus it can also vary substantially between cardiac and noncardiac disease states.

THE RELATIONSHIP BETWEEN GLUCOSE VARIABILITY AND PATIENT OUTCOMES DURING ACUTE CORONARY SYNDROME

Although mean and admission glucose levels are associated with higher risk of mortality during ACS, these metrics do not capture the variability in glucose values during hospitalization. Physiologic studies have suggested several mechanisms through which glucose variability may adversely affect prognosis in the setting of ACS, including oxidative stress and cytokine release, among others.[55,56] In addition, glucose variability has been associated with adverse events in other critically ill patient populations.[57–59] Several recent studies have examined the association of various glucose variability metrics with prognosis in patients with ACS. In the analysis of over 18,000 patients hospitalized with ACS across 61 U.S. hospitals, five different metrics of glucose variability were evaluated for their association with in-hospital mortality.[60] Although greater glucose variability was associated with increased risk of in-hospital mortality in unadjusted analyses, it was no longer independently predictive (regardless of the metric used) after multiple patient factors were controlled for, including mean blood glucose levels. In contrast, mean blood glucose remained an important independent predictor of survival. These findings suggest that glucose variability does not provide additional prognostic value above and beyond already recognized risk factors for mortality during ACS; the findings were further validated by the recent analysis of the DIGAMI-2 study, which also showed no relationship between glucose variability and survival.[61]

THE PROGNOSTIC IMPORTANCE OF HYPOGLYCEMIA IN PATIENTS WITH ACUTE CORONARY SYNDROME

Because therapy for hyperglycemia in the hospital necessitates the use of insulin, it is expected that glucose lowering in the inpatient setting will produce excess hypoglycemia. Several studies have suggested that glucose values in the hypoglycemic range may adversely affect mortality in ACS (93% increase in the adjusted odds of 2-year mortality in one study)[25,62] and have demonstrated a J-shaped relationship between average glucose values during hospitalization and in-hospital mortality (see **Fig. 20-1**).[21] Whether hypoglycemia is directly harmful in patients with ACS or whether it is simply a marker for the most critically ill patients was evaluated in a large observational study.[63] The authors showed that the risk associated with low blood glucose was confined to those who developed hypoglycemia spontaneously, most likely as the result of severe underlying illness. In contrast, hypoglycemia that occurred after insulin initiation was not associated with worse survival. Two subsequent analyses of data from the DIGAMI-2 and CREATE-ECLA trials also found no significant association between hypoglycemia and mortality, after adjustment for confounders.[64,65] These findings suggest that hypoglycemia is a marker of severe illness rather than a direct cause of adverse outcomes. Although continuous efforts to avoid hypoglycemia are certainly warranted, these studies cast some doubt on the



Insulin use among patients hospitalized for AMI with severe persistent hyperglycemia **A,** Overall cohort. **B,** Across hospitals.

FIGURE 20-3 **The rates of treatment with insulin in patients hospitalized with ACS across mean hospitalization glucose levels.** *(Modified from Venkitachalam L, McGuire DK, Gosch K, et al: Temporal trends and hospital variation in the management of severe hyperglycemia among patients with acute myocardial infarction in the United States,* Am Heart J *166:315-324, 2013.)*

assumption that the lack of clinical benefit from intensive glycemic control in clinical trials is simply a consequence of excess hypoglycemia.

CURRENT PATTERNS OF GLUCOSE CONTROL IN ACUTE CORONARY SYNDROME

The current practice of glucose management in the United States is highly variable.[28] Large proportions of ACS patients with hyperglycemia do not receive glucose-lowering therapy, even in the setting of marked hyperglycemia; this is particularly evident among those without known diabetes.[7,26] A study from the United Kingdom showed that 64% of patients without diabetes with admission glucose of 11 mmol/L (approximately 200 mg/dL) or higher received no glucose-lowering treatments during hospitalization.[66] Similar findings were observed in the recent analysis of 4297 admissions of patients with ACS and mean hospitalization glucose of 200 mg/dL or higher; insulin was used 63% of the time, and IV insulin infusion was used in only 13% of these admissions, with substantial variation among hospitals that did not change over 10 years of observation (**Fig. 20-3**).[67] Many factors contribute to this inconsistency of clinical practice, such as the lack of convincing clinical outcomes data; concerns about hypoglycemia; institutional barriers; and clinical inertia, underscoring the critical importance of continued investigation with regard to the efficacy and safety of glucose management in the setting of ACS.

SUMMARY AND RECOMMENDATIONS

There is a clear and urgent need for well-designed, large-scale clinical outcomes trials of target-driven glucose control in ACS with sufficient statistical power to detect a clinically important difference in mortality and other adverse clinical outcomes. Until such trials are completed, any specific recommendations with regard to glucose management in ACS are based on epidemiologic observations, mechanistic hypotheses, and expert consensus, and not grounded in solid clinical evidence.

Reflecting this uncertainty, in 2008 the AHA published an update on its position regarding glucose targets for ACS-MI patients, which substantially liberalized previous recommendations.[22] This AHA position advocates for a glucose treatment threshold of higher than 180 mg/dL. A similar position was adopted by the 2009 focused update of STEMI guidelines[68] and the 2012 focused update of NSTEMI guidelines[69] and was also endorsed by the revised American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA) guidelines.[70] These guidelines now recommend the same glucose threshold for therapeutic intervention in critically ill patients—higher than 180 mg/dL—with a suggested therapeutic target of glucose control specified at 140 to 180 mg/dL, a substantially more liberal approach than proposed in prior documents.[48] Although even these targets represent an expert consensus, it is likely the most prudent approach in the presence of the accumulated data.

Until more information becomes available, several practical suggestions are reasonable with regard to glucose management during ACS hospitalization:

1. Assessment of glucose values at the time of admission and glucose monitoring during hospitalization will provide useful information with regard to risk stratification and prognosis. Thus such assessment and monitoring should be pursued regardless of whether treatment is being considered.
2. If targeted glucose control is being considered, several precautions should be observed:
 a. Conservative treatment initiation thresholds and glucose targets (as outlined earlier) should be used, in line with the recommendations of professional societies. Very aggressive glucose lowering, including "normalization of blood glucose" as previously recommended, does not clearly offer additional benefit and may be harmful.
 b. Evidence-based protocols should be used when and if glucose control strategies are implemented. Such protocols should:
 i. have demonstrated effectiveness and safety with regard to targeted glucose control in the variety of clinical settings
 ii. incorporate the rate of change in glucose values as well as insulin sensitivity in determination of insulin infusion rates and adjustments
 iii. provide specific directions regarding the frequency of glucose testing and hypoglycemia management

Last, and most important, continued efforts are necessary for the design and execution of definitive clinical trials assessing glucose control targets, therapies, and timing, so that more evidence-based recommendations may be provided to clinicians with regard to glucose management in patients with ACS.

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21 Antiplatelet and Antithrombotic Therapy in Diabetic Patients with Acute Coronary Syndrome

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Patients with diabetes mellitus (DM) and acute coronary syndrome (ACS) are at particularly high risk for recurrent cardiovascular events and death. The reason for this increased risk is multifactorial, including a higher risk profile, higher platelet reactivity, and underuse of evidence-based medications in these patients.[1] This chapter includes a summary and review of antiplatelet and antithrombotic therapies that are approved in the United States and in Europe for clinical use in patients with ACS.

PLATELET AGGREGATION

Patients with diabetes, particularly those with type 2 diabetes (T2DM), exhibit increased platelet reactivity and a reduced inhibition in response to platelet inhibitors. There is also evidence that platelet activation is directly affected by hyperglycemia and insulin resistance. Platelets are affected by insulin because of the presence of insulin receptor subtypes on the platelet surface.[2] Activation of these receptors leads to suppression of cyclic adenosine monophosphate (cAMP), resulting in inhibition of P2Y12 receptors and decreased calcium influx, thus inhibiting platelet activity. In case of insulin resistance, platelets display increased calcium influx and thereby activation of the P2Y12 receptor.[3] High platelet reactivity (HPR) is well documented in patients with diabetes[4] and may contribute to the high incidence of cardiovascular disease and poor outcomes in this population. Thromboxane A_2 (TXA_2), the most potent vasoconstrictor that is secreted from platelets after activation, is circulating in higher amounts in patients with T2DM.[5] Another abnormality of platelets in patients with T2DM is an increased platelet expression of P-selectin and of the glycoprotein IIb/IIIa receptor (GP IIb/IIIa) (**Fig. 21-1**).[6]

Platelet adhesion, activation, and aggregation play a pivotal role in atherothrombosis in patients with and without DM. Intracoronary atherothrombosis is the most common cause of the development of ACS and plays a central role in complications occurring around percutaneous coronary intervention (PCI), including recurrent ACS, procedure-related myocardial infarction (MI), and stent thrombosis.[7] Inhibition of platelet aggregation by medical treatment impairs formation and progression of thrombotic processes and is therefore of great importance in the prevention of complications after ACS or associated with PCI (**Fig. 21-2**).[8,9]

PLATELET INHIBITION

Antiplatelet agents include cyclooxygenase (COX) inhibitors such as aspirin, which block the production of TXA_2; GP IIb/IIIa receptor blockers such as abciximab, eptifibatide, and tirofiban, which inhibit fibrin-mediated platelet activation; and thienopyridines such as clopidogrel, prasugrel, cangrelor, ticagrelor, and ticlopidine, which bind to and antagonize P2Y12 receptors. Optimizing dual antiplatelet therapy (DAT) with combinations of agents from these classes may improve cardiovascular disease outcomes in patients with diabetes and ACS events (**Tables 21-1** and **21-2**).

Aspirin

The mechanism of action of aspirin occurs through permanent inactivation of the COX activity of prostaglandin H synthase 1 (PGH_1) and PGH_2 (also referred to as COX-1 and COX-2) (**Fig. 21-3**).[10] These isoenzymes catalyze the conversion of arachidonic acid to PGH_2. PGH_2 is in turn a substrate for several tissue-specific isomerases that generate several bioactive prostanoids, including TXA_2 and prostacyclin (prostaglandin I_2 [PGI_2]). Low levels of aspirin predominately inhibit COX-1, whereas higher levels are needed to also inhibit COX-2.[11] TXA_2 is mainly derived from COX-1, and PGE_1 mainly from COX-2 (see **Fig. 21-3**).

Aspirin has been considered the mainstay of treatment of all patients with ACS and is recommended with a high level of evidence in current international guidelines.[12,13]

In the setting of ACS, long-term low-dose aspirin treatment (75 to 100 mg/day) is recommended, with support from a meta-analysis.[14] Although a recent small study suggested that more frequent administration would be beneficial in patients with DM,[15] the large Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial including almost 6000 patients with DM was not able to show that a high dose of aspirin was superior to a low dose.[16] More recent trials have also shown that modifications of clinical care based on the use of platelet function testing for aspirin responsiveness do not improve outcome.[17] The optimal dose of aspirin when used in combination with other platelet inhibitors in the setting of acute and long-term treatment of patients with ACS, with stable coronary artery disease, or after PCI with or

without DM has not yet been clearly defined from large randomized controlled trials. Based on published data and tablet availability, the recommended dose should be 75 to 100 mg in patients with or without DM.

ADP Receptor Blockers

An essential part in the platelet activation process is the interaction of adenosine diphosphate (ADP) with the platelet P2Y12 receptor (see also **Chapter 16**).[7] The P2Y12 receptor is the predominant receptor involved in the ADP-stimulated activation of the GP IIb/IIIa receptor.[10] Activation of the GP IIb/IIIa receptor results in enhanced platelet degranulation and thromboxane production and prolonged platelet aggregation.[11] Thienopyridines and non-thienopyridine ADP receptor blockers inhibit the platelet activation and aggregation by antagonizing the thrombocyte P2Y12 receptor. This prevents the binding of ADP to the receptor, which attenuates platelet aggregation and reaction of thrombocytes to stimuli of thrombus aggregation such as thrombin (**Table 21-3**).[4]

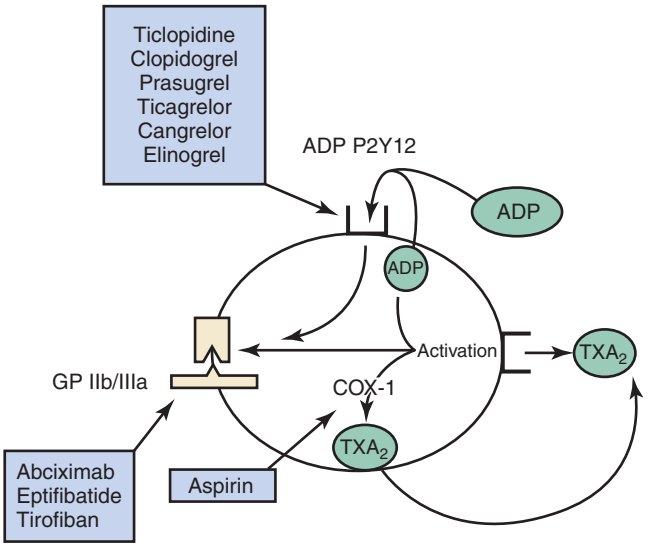


FIGURE 21-1 Platelet activation. ADP = Adenosine diphosphate; COX-1 = cyclooxygenase 1. *(Modified from Capodanno D, Corrado T, Angiolillo D: Update on novel P2Y12 inhibitors: focus on prasugrel, ticagrelor, cangrelor and elinogrel.* E-Journal of the European Society of Cardiology Council for Cardiology Practice, *8(21), February 10, 2010. Available at: www.escardio.org/communities/councils/ccp/e-journal/volume8/Pages/P2Y12-inhibitors-Capodanno.aspx#.UxejcPldVyw.)*

Clopidogrel

Although clopidogrel combined with aspirin has been used successfully to prevent thrombotic events in patients with ACS, patients with DM, when compared with those without, have consistently been shown to have higher on-treatment platelet reactivity and worse clinical outcomes. The mechanisms leading to poor response to clopidogrel in patients with DM are not fully elucidated but are likely multifactorial, including genetic, metabolic, cellular, and clinical factors. Clopidogrel, a prodrug, requires a two-step hepatic cytochrome P-450 (CYP450) metabolic activation to produce the active metabolite that inhibits the platelet P2Y12 receptor.[13] Before intestinal absorption, 85% of the prodrug is hydrolyzed by esterases to an inactive carboxylic acid derivate. Because of these pharmacodynamic characteristics of clopidogrel, several hours pass between ingestion and attainment of therapeutic levels. This results in suboptimal platelet aggregation inhibition during acute PCI for ACS and a higher risk for acute stent thrombosis. Moreover, the longer period up to therapeutic levels may raise the bleeding risk during acute coronary artery bypass grafting (CABG), if necessary based on coronary anatomy. In addition, there is substantial variability in clopidogrel response among patients. Accumulating evidence shows that a suboptimal response to clopidogrel is associated with worse clinical outcomes such as coronary ischemia or stent thrombosis.[14–17] This suboptimal therapeutic response is particularly salient

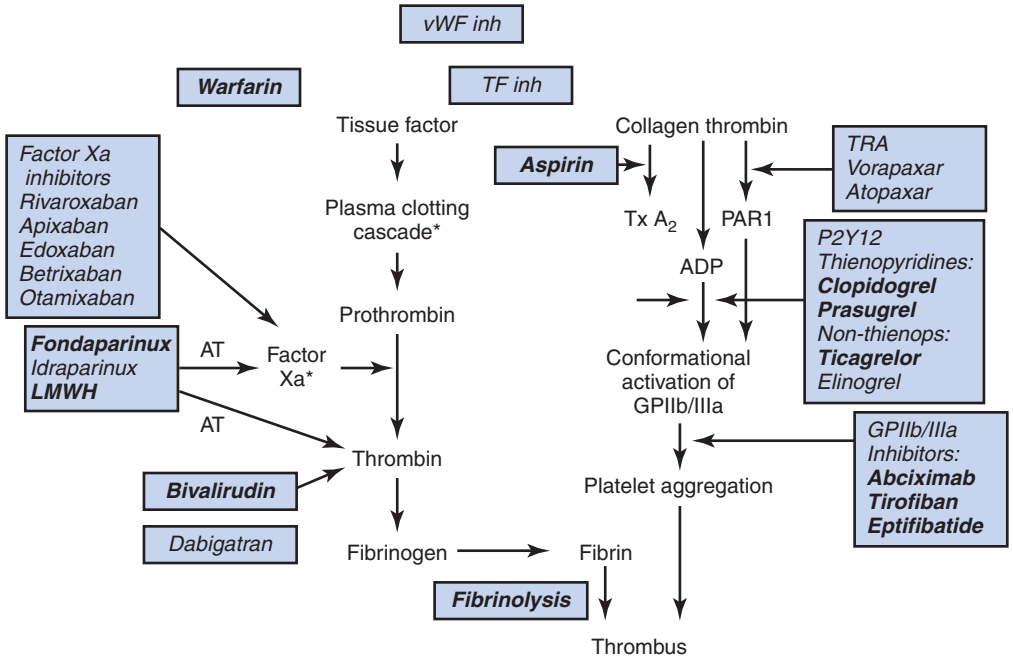


FIGURE 21-2 Targets for antithrombotic treatment. Agents approved for ACS treatment are shown in bold. AT = Antithrombotic treatment; LMWH = low molecular weight heparin; PAR1 = protease receptor activator 1; TF = tissue factor; TRA = thrombin receptor antagonist; vWF = von Willebrand factor.

TABLE 21-1 Approved Agents for Acute Coronary Syndromes

AGENT	ANTITHROMBOTIC ACTION	MECHANISM OF ACTION	TYPE OR FAMILY	MODE OF ADMINISTRATION
Aspirin	Antiplatelet	Cyclooxygenase inhibitor		Oral
Clopidogrel	Antiplatelet	P2Y12 receptor inhibitor	Thienopyridine	Oral
Prasugrel	Antiplatelet	P2Y12 receptor inhibitor	Thienopyridine	Oral
Ticagrelor	Antiplatelet	P2Y12 receptor inhibitor	Cyclopentyl-triazolo-pyrimidine	Oral
Abciximab	Antiplatelet	GP IIb/IIIa inhibitor	Monoclonal antibody	Intravenous
Tirofiban	Antiplatelet	GP IIb/IIIa inhibitor	Peptide	Intravenous
Eptifibatide	Antiplatelet	GP IIb/IIIa inhibitor	Nonpeptide	Intravenous
Unfractionated heparin	Anticoagulant	Antithrombin (IIa) potentiator		Intravenous or subcutaneous
Enoxaparin	Anticoagulant	Xa/IIa (antithrombin) inhibitor		Intravenous or subcutaneous
Fondaparinux	Anticoagulant	Xa inhibitor		Intravenous or subcutaneous
Bivalirudin	Anticoagulant	Thrombin inhibitor		Intravenous
Warfarin	Anticoagulant	Vitamin K antagonist		Oral

TABLE 21-2 Common Oral Antiplatelet Agents and Doses in Patients with Acute Coronary Syndrome (ACS)

ANTIPLATELET AGENT	LOADING DOSE	WHEN TO GIVE	REGULAR DOSE	SPECIAL SITUATIONS
Aspirin	300 mg oral; 80-150 mg IV	Before or at cath	75-100 mg daily oral	
Clopidogrel	600 mg oral	Before or at cath	75 mg daily oral	
Prasugrel	60 mg	After cath for NSTE-ACS Before or at cath for STE-ACS	10 mg daily oral	Only age older than 75, weight <60 kg (consider 5 mg daily regular dose); contraindicated if history of stroke or TIA
Ticagrelor	180 mg	Before or at cath	90 mg bid oral	

cath = Catheterization; *NSTE-ACS* = non–ST-elevation acute coronary syndrome; *STE-ACS* = ST-elevation acute coronary syndrome; *TIA* = transient ischemic attack.

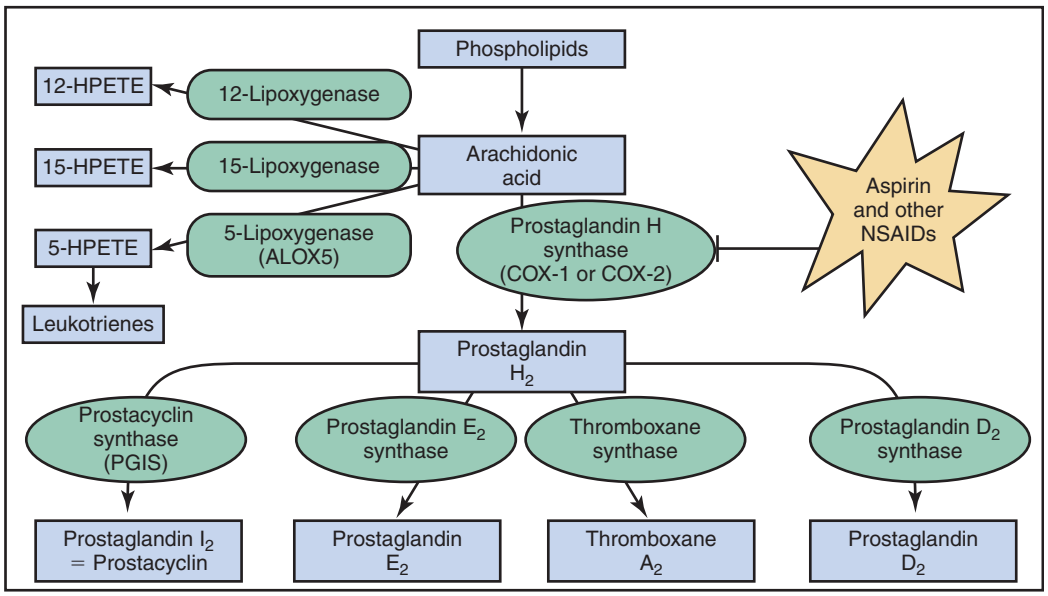


FIGURE 21-3 Mechanism of action of aspirin is through inhibition of COX enzymes. ALOX5 = Arachidonic 5-lipoxygenase; HPETE = hydroperoxyeicosatetraenoic acid; NSAIDs = nonsteroidal anti-inflammatory drugs. *(Modified from Ulrich and colleagues, 2006; Gupta and DuBois, 2001.)*

in patients with diabetes. A reduced generation of the active clopidogrel metabolite may contribute to poor clopidogrel responsiveness in patients with DM.[18] A large part of the variability in the clopidogrel response is a consequence of the variation in the *CYP* gene.[18] This gene codes for the CYP-450 enzymes involved in the biotransformation of the prodrug clopidogrel to the active metabolite. Particularly, polymorphisms in the CYP2C19 allele are associated with a reduced activity of clopidogrel. Poor response based on CYP2C19 genotype can be partly reversed by a higher dose.[19]

TABLE 21-3 Major P2Y12 Receptor Inhibitor Trials

TRIAL	POPULATION	COMPARATOR	PRIMARY ENDPOINT	MORTALITY	MI	CVA	STENT THROMBOSIS	BLEED
Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) (2001)	12,562 NSTE-ACS	Clopidogrel 75 mg (300 mg loading) versus placebo	CV death, MI, CVA Clopidogrel 9.3% Placebo 11.4% ($P<0.001$) ARR 2.1%; RRR 20%; NNT 48	CV death Clopidogrel 5.1% Placebo 5.5% ($P=$NS)	Clopidogrel 5.2% Placebo 6.7% (P not given)	Clopidogrel 1.2% Placebo 1.4% (P not given)	NA	Major* bleed Clopidogrel 3.7% Placebo 2.7% ($P=0.001$) NNH 100
CURRENT-OASIS (2010)	25,086 (invasive strategy) NSTE-ACS 63% STEMI 37%	Clopidogrel (600 mg loading, 150 mg days 2-7, then 75 mg) versus 150 mg loading, then 75 mg	CV death, MI, CVA (at 30 days) Double 4.2% Standard 4.4% ($P=.30$)	CV death Double 2.1% Standard 2.2% All-cause mortality Double 2.3% Standard 2.4%	Double 1.9% Standard 2.2% ($P=0.09$)	Double 0.5% Standard 0.5% ($P=.95$)	NA	Major† bleed Double 2.5% Standard 2.0% ($P=0.01$) NNH 200
TRITON-TIMI 38 (2007)	13,608 undergoing PCI NSTE-ACS 74% STEMI 26%	Prasugrel 10 mg (60 mg loading) versus clopidogrel 75 mg (300 loading)	CV death, MI, CVA Prasugrel 9.9% Clopidogrel 12.1% ($P<0.001$) ARR 2.2%; RRR 27%; NNT 46	CV death Prasugrel 2.1% Clopidogrel 2.4% ($P=.31$) Any cause Prasugrel 3.0% Clopidogrel 3.2% ($P=.64$)	Prasugrel 7.3% Clopidogrel 9.5% ($P<0.001$)	Prasugrel 1.0% Clopidogrel 1.0% ($P=0.93$)	Prasugrel 1.1% Clopidogrel 2.4% ($P<0.001$)	Non–CABG-related major‡ bleed Prasugrel 2.4% Clopidogrel 1.8% ($P=0.03$) NNH 167 CABG-related major bleed Prasugrel 13.4% Clopidogrel 3.2% ($P<0.001$) NNH 10
TRILOGY (2012)	7243 patients with noninvasive ACS younger than age 75	Prasugrel (10 mg daily) versus clopidogrel (75 mg daily)	CV death, MI, CVA Prasugrel 13.9% and clopidogrel 16.0% ($P=0.21$)	CV death Prasugrel 6.6% Clopidogrel 6.8% ($P=0.48$)	Prasugrel 8.3% Clopidogrel 10.5% ($P=0.21$)	Prasugrel 1.5% Clopidogrel 2.2% ($P=0.08$)	NA	Major‡ bleed Prasugrel 2.1% Clopidogrel 1.5% ($P=0.27$)
Study of Platelet Inhibition and Patient Outcomes (PLATO) (2009)	18,624 NSTE-ACS 59% STEMI 38% (invasive and noninvasive)	Ticagrelor 90 mg bid (180 mg loading) versus clopidogrel 75 mg (300-600 mg loading)	Death from vascular causes, MI, CVA Ticagrelor 9.8% Clopidogrel 11.7% ($P<0.001$) ARR 1.9%; RRR 16%; NNT 53	Vascular causes Ticagrelor 4.0% Clopidogrel 5.1% ($P=0.001$) Any cause Ticagrelor 4.5% Clopidogrel 5.9% ($P<0.001$)	Ticagrelor 5.8% Clopidogrel 6.9% ($P=0.005$)	Ticagrelor 1.5% Clopidogrel 1.3% ($P=0.22$)		Major§ bleed Ticagrelor 11.6% Clopidogrel 11.2% ($P=0.43$) NNH: NA Non-CABG bleeding Ticagrelor 4.5% Clopidogrel 3.8% ($P=0.03$) NNH 143

ARR = Absolute risk reduction; CABG = coronary artery bypass grafting; CV = cardiovascular; CVA = cerebrovascular accident; NA = not available; NNH = numbers needed to harm; NNT = numbers needed to treat; NS = non significant; RRR = relative risk reduction; STEMI = ST-segment elevation myocardial infarction.

Clopidogrel has undergone large phase III trials in more than 100,000 patients, demonstrating its efficacy across a spectrum of atherosclerotic conditions, and its use is supported in guidelines for ACS,[8,9,12] ischemic stroke,[20] and peripheral artery disease.[21] No significant treatment-by-diabetes status interactions with the respective primary composite outcomes were found in the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,[22] the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,[23] or the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,[24] suggesting similar efficacy and safety of clopidogrel for those with as for those without diabetes.

Although clopidogrel combined with aspirin has been used successfully to prevent thrombotic events in patients with ACS,[23] patients with DM have consistently been shown to have higher on-treatment platelet reactivity and worse clinical outcomes.[4,25] Still, a high dose of clopidogrel was not superior to a standard dose of clopidogrel in the CURRENT-OASIS 7 trial, with no interaction by diabetes status.[16] Therefore novel and more potent platelet inhibitors have been recommended, particularly in patients with DM.[12]

Prasugrel

Prasugrel is a third-generation thienopyridine. Rapidly after ingestion, prasugrel is hydrolyzed in the gastrointestinal system into an intermediary metabolite. This intermediary metabolite is hepatically activated in a single step and forms an active metabolite that binds to the P2Y12 receptor on the platelet. This irreversible bond with the receptor inhibits activation and aggregation of the platelet.[18] The peak concentration of the active metabolite of prasugrel is reached after 30 minutes, and the final concentration is linearly dependent on the prasugrel dose, which varies between 5 (low-dose maintenance) and 60 mg (oral loading dose). If not bound to the receptor, active metabolites have a half-life of approximately 7 hours.[18] A maximum of 60% to 70% platelet inhibition is usually achieved within 2 to 4 hours.[11]

Prasugrel has been investigated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38).[26] In this trial, 13,608 patients with moderate- and high-risk ACS were randomized to prasugrel (60-mg loading dose and 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for a median of 15 months. Randomization took place after coronary angiography and before PCI (in patients with ST-elevation myocardial infarction [STEMI] randomization before angiography was allowed). The use of prasugrel was associated with a significant reduction of the main efficacy endpoint (cardiovascular death, nonfatal MI, or nonfatal stroke). This was mainly driven by a reduction in MI and stent thrombosis with no difference in mortality. However, the reduction in ischemic endpoints with prasugrel was accompanied by a higher incidence of major bleeding events. In an exploratory analysis, three subgroups of interest were identified that had less clinical efficacy and greater absolute levels of bleeding than the overall cohort, resulting in less net clinical benefit or in clinical harm. These included patients with a history of stroke or transient ischemic attack, patients aged 75 years and older, and patients with a body weight of less than 60 kg.

Prasugrel compared with clopidogrel administered after angiography reduced the primary endpoint of cardiovascular death, MI, or stroke by 4.8% (30% relative risk reduction) in diabetic patients in a subgroup analysis of the TRITON-TIMI 38 trial,[27] with no statistically significant interaction for the primary outcome by DM status or by diabetes type. There was a numeric reduction of cardiovascular death and a marked reduction of MI and stent thrombosis with prasugrel versus clopidogrel in diabetic patients. Furthermore, there was a differential increase in bleeding risk in patients with and without diabetes with no significant increase in major bleeding events in the diabetes group (**Fig. 21-4**).

In the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial,[31] treatment with prasugrel (10 mg daily) versus clopidogrel (75 mg daily) was evaluated in 7243 patients under the age of 75 years with ACS selected for a final treatment strategy of medical management without revascularization within 10 days after the index event. At a median follow-up of 17 months, the primary endpoint of death from cardiovascular causes, MI, or stroke was not significantly reduced and there was no interaction for diabetes status.

Ticagrelor

Ticagrelor is an oral nonthienopyridine P2Y12-inhibiting agent with a reversible and direct action on the receptor that provides faster, greater, and more consistent platelet inhibition than clopidogrel.[28] The compound is orally active

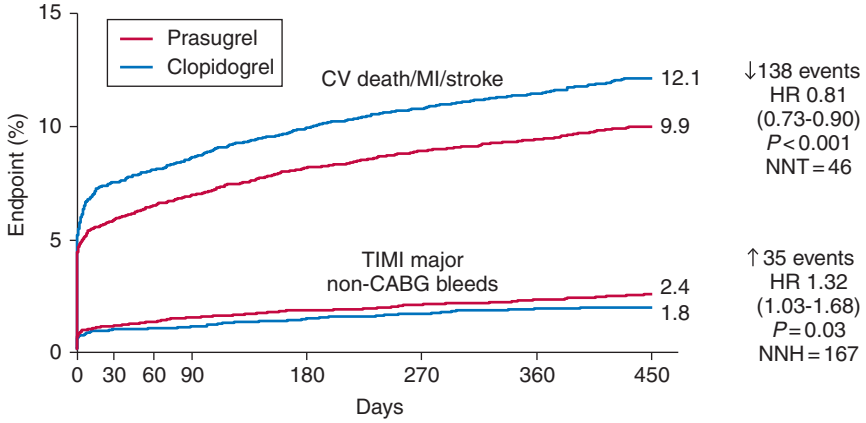


FIGURE 21-4 TRITON-TIMI 38 efficacy and safety (net clinical benefit). HR = Hazard ratio. *(Modified from Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes,* N Engl J Med *357:2001-2015, 2007.)*

without the requirement of metabolic activation.[27] It undergoes enzymatic degradation to at least one active metabolite which is approximately as potent as its parent compound.[27] The maximum plasma concentration and maximum platelet inhibition are reached 1 to 3 hours after oral administration, and the plasma half-life is 6 to 13 hours.[11]

Ticagrelor was compared with clopidogrel in 18,624 patients with ST-elevation acute coronary syndrome (STE-ACS) or non–ST-elevation acute coronary syndrome (NSTE-ACS) in the multicenter randomized Study of Platelet Inhibition and Patient Outcomes (PLATO).[29] Patient randomization took place as early as possible after the index event. Patients on maintenance and those who had received a loading dose of clopidogrel were allowed in the trial. After randomization, the patients received ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300- to 600-mg loading dose, 75 mg daily thereafter). All patients received aspirin unless intolerant. There was a significant reduction of the primary outcome of cardiovascular death, MI, or stroke at 12-month follow-up driven by lower cardiovascular mortality, MI, and stent thrombosis rates (**Fig. 21-5**).

A prespecified substudy from the PLATO trial showed that DM and higher levels of glucose and hemoglobin A1c (HbA1c) were strongly associated with all evaluated ischemic and bleeding endpoints. Ticagrelor compared with clopidogrel reduced cardiovascular death, MI, or stroke as well as total mortality and stent thrombosis consistently and irrespective of diabetic status, insulin treatment, and glycemic control (**Table 21-4**).[30.]

Glycoprotein IIb/IIIa Inhibitors

Activation of the GP IIb/IIIa receptor is considered the final common pathway in platelet aggregation. Blocking this receptor almost completely abolishes aggregation of platelets. Three agents are available on the market: abciximab, tirofiban, and eptifibatide. Abciximab is the Fab fragment of a monoclonal antibody 7E3, eptifibatide a peptide, and tirofiban a nonpeptide receptor antagonist. Each binds with strong affinity to the GP IIb/IIIa receptor. GP IIb/IIIa receptor inhibitors have consistently been shown in a large number of trials to reduce the rate of procedure-related MI in patients undergoing percutaneous interventions.[32–36] Long-term mortality is reduced in patients treated with abciximab and heparin in conjunction with coronary stenting as compared with patients treated solely with heparin.[37] Furthermore, GP IIb/IIIa inhibitors, added to background therapy with aspirin and heparin, reduce the rate of the composite of death and MI in patients with non-ST-segment elevation MI (NSTEMI).[30,38–40] The benefit has been shown to be most pronounced in high-risk patients with elevated troponin levels[41,42] and in patients treated with early coronary interventions.[43,44]

The efficacy of the GP IIb/IIIa inhibitors in ACS patients with T2DM has been proven by a pooled meta-analysis.[45] GP IIb/IIIa inhibitor use resulted in a 22% reduction of 30-day mortality compared with those with no GP IIb/IIIa inhibitor use.[46] These positive data were generated years ago when modern stents and optimal accompanying pharmacologic treatment, including the new antiplatelet agents, were not available. The European Society of

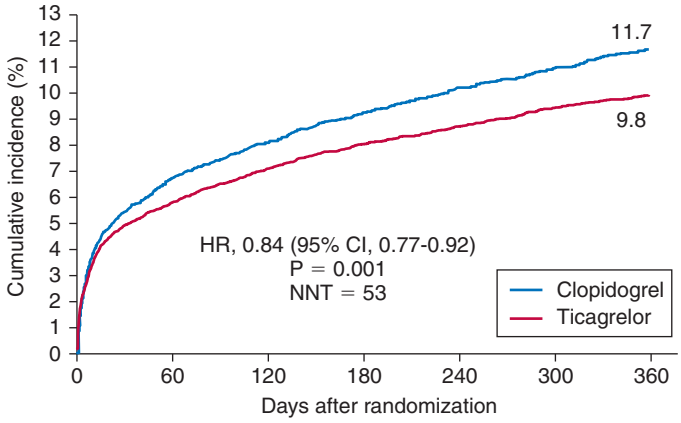


FIGURE 21-5 PLATO: K-M estimate of time to first primary efficacy event (composite of CV death, MI, or stroke). CI = Confidence interval; HR = hazard ratio; K-M = Kaplan-Meier; NNT = number needed to treat. *(Modified from Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes,* N Engl J Med *361:1045-1057, 2009.)*

TABLE 21-4 Comparison of P2Y12 Inhibitors

DRUG	ROUTE	METABOLIC ACTIVATION	CYP450	TYPICAL DOSE	BINDING	HALF-LIFE
Ticlopidine	PO	Required	Yes	500 mg load, then 250 mg bid	Irreversible	12 hr
Clopidogrel	PO	Required	Yes	300-600 mg load, then 75 mg daily	Irreversible	7-8 hr
Prasugrel	PO	Required	Yes	60 mg load, then 10 mg daily	Irreversible	2-15 hr
Cangrelor	IV	None	No	30 µg/kg, bolus, 4 µg/kg min drip	Reversible	2-3 min
Ticagrelor	PO	None	No	180 mg load, then 90 mg bid	Reversible	7-8 hr

Data from Michelson AD: New P2Y12 antagonists, *Curr Opin Hematol* 16:371-377, 2009.

Cardiology (ESC) and ACC/AHA guidelines for patients with NSTE-ACS who are already treated with DAT recommend the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) if the risk of bleeding is low.[12]

COAGULATION INHIBITION

Several studies have shown a direct relationship between elevated circulating glucose and insulin levels and coagulation markers.[47] Patients with T2DM display high levels of plasminogen activator inhibitor type 1 (PAI-1), fibrinogen, tissue factor procoagulant activity, and coagulation factor VII and VIII and higher thrombin-antithrombin complex, as reviewed in **Chapter 10** (**Table 21-5**).

Unfractionated Heparin and Low-Molecular-Weight Heparin

Unfractionated heparin (UFH) is a heterogeneous mixture of sulfated polysaccharides of varying chain length increasing the effects of antithrombin, with the key antithrombotic effects by inhibition of thrombin. Low-molecular-weight heparins (LMWHs) are fragments of UFH that possess a greater anti-Xa activity in relation to anti-IIa (antithrombin) than UFH. In addition, LMWHs have several potential advantages over UFH.[48,49] The dose response is more predictable and reliable, the immunogenicity is reduced with less frequent thrombocytopenia, and finally there is less rebound effect after discontinuation of therapy. Other advantages from a practical point of view include a longer biologic half-life, enabling easier administration with subcutaneous injections and less need for monitoring the anticoagulant effect. LMWH has been shown to be at least as effective as UFH in the short-term. Recently, the Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up (ATOLL) trial investigated an acute half-dose regimen of enoxaparin (0.5 mg/kg) versus the usual dose of UFH in patients with ACS during PCI.[50] In this study, enoxaparin nonsignificantly reduced the composite primary clinical endpoint (death, MI, procedure failure, and severe bleeding) and was statistically superior to UFH with respect to secondary ischemic endpoints without increasing the bleeding risk. This benefit was independent of diabetes status.[50]

Fondaparinux

Fondaparinux is a pentasaccharide that binds reversibly to antithrombin III with high affinity and therefore catalyzes the antithrombin III–mediated inhibition of factor Xa, thus preventing thrombin formation. A single daily dose of fondaparinux is sufficient for its full action, and there is no need for laboratory monitoring because of the long elimination half-life of approximately 17 to 21 hours and the very low interindividual and intraindividual variability in pharmacokinetics. The OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial[51] investigated fondaparinux versus enoxaparin in patients with NSTEMI and found noninferiority for ischemic events but a significant lower bleeding risk with fondaparinux treatment. This had a short- and long-term statistically significant favorable impact on hard clinical endpoints—that is, cardiovascular death, MI, and stroke. Also, in a subgroup analysis of the diabetic patient cohort, fondaparinux was superior to enoxaparin. For patients with STEMI, fondaparinux was tested against UFH.[52] Fondaparinux was significantly superior to UFH for those patients treated conservatively (without reperfusion)[53] and for those treated with thrombolysis (fibrin-specific and nonspecific agents), but not for patients referred for primary

TABLE 21-5 Common Parenteral Anticoagulants and Doses in Patients Treated with Acute Coronary Syndrome (ACS)

PARENTERAL ANTICOAGULANT	INTRAVENOUS BOLUS	WHEN TO GIVE IN RELATION TO PCI	PROLONGATION OF THERAPY AFTER PCI	SPECIAL CONSIDERATIONS
UFH	70-100 U/kg 50-60 U/kg if IIb/IIIa	Before or at cath	Only if other indication (e.g., mechanical valve)	
Enoxaparin	0.5 mg/kg bolus for PCI	Before or at cath	1 mg/kg every 12 hr SC for 8 days or until discharge without PCI	Creatinine clearance <30 mL/min—1 mg/kg every 24 hr SC
Fondaparinux		Before cath	2.5 mg intravenous bolus followed by subcutaneous dose of 2.5 mg once daily up to 8 days or until hospital discharge	Additional UFH (50 U/kg) for cath required
Bivalirudin	0.75 mg/kg	Before or at PCI	1.75 mg/kg/hr	Lower initial infusion rate (1.4 mg/kg/hr) if GFR 30-59 mL/min) Contraindicated if GFR <30 mL/min and in dialysis-dependent patients
Abciximab	0.25 mg/kg	At PCI for NSTE-ACS Possibly before PCI for STEMI	0.125 μg/kg/min up to 12 hr	
Eptifibatide	180 μg/kg	At PCI for NSTE-ACS Possibly before PCI for STEMI	2 μg/kg/min for at least 12 hr	Creatinine clearance <50 mL/min—additional 180 μg/kg intravenous bolus then 1 μg/kg/min infusion
Tirofiban	25 μg/kg	At PCI for NSTE-ACS Possibly before PCI for STEMI	0.15 μg/kg/min up to 18 hr	Creatinine clearance <60 mL/min—0.075 μg/kg/min infusion after loading

GFR = Glomerular filtration rate; UFH = unfractionated heparin.

PCI. Fondaparinux has the highest level of recommendation in the recently released NSTEMI guidelines from the ESC.[20] None of these trials has shown any interaction by diabetes status for efficacy on clinical outcomes.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor, and in contrast to heparins, it also inhibits clot-bound thrombin. Because of a very short plasma half-life of 25 minutes and a preferential renal elimination of its inactive metabolites, accumulation in case of renal failure and subsequently the bleeding risk is lower compared with heparins. In contrast to UFH, bivalirudin is not neutralized by platelet factor 4, a mechanism that is responsible for heparin-induced thrombocytopenia, and therefore not associated with this serious drug-related adverse effect. The dosage of bivalirudin is weight dependent. Bivalirudin has been investigated in patients undergoing elective PCI as well as in ACS (NSTEMI and STEMI) patients.[54–57] Bivalirudin with provisional use of UFH and GP IIb/IIIa inhibitors had similar anti-ischemic properties compared with standard treatment with GP IIb/IIIa inhibitors plus UFH, but with significantly lower bleeding risk. In the long term, the bivalirudin strategy also reduced mortality rates.[58] However, bivalirudin was associated with an increased risk for acute stent thrombosis in the early phase of treatment after primary PCI. Because T2DM is a significant predictor of early stent thrombosis,[59] a longer duration of bivalirudin administration after PCI (up to 4 hours) in the setting of ACS and especially in patients with diabetes is proposed.

SUMMARY

Patients with diabetes versus those without diabetes who experience an ACS event have a worse prognosis. Despite several new therapeutic agents that have gradually improved treatment of ACS in patients with diabetes, patients with diabetes still have a higher mortality risk compared with patients without diabetes. More research is needed to identify the optimal antithrombotic strategy and duration of therapy. Patients with diabetes have the same relative benefit from all recommended antithrombotic therapies as patients without diabetes; but when one considers the high absolute event rate, the absolute benefit is considerably greater, translating into a lower "number needed to treat" for derivation of benefit. Therefore, more attention should be focused on implementing therapies that have been shown to lower clinical events and mortality in this high-risk population.

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22 Role of Primary Invasive Strategy and Revascularization in Diabetic Patients with Acute Coronary Syndromes



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In patients with diabetes mellitus, the risk of developing coronary artery disease is increased by twofold to fourfold compared with patients without diabetes.[1,2] Moreover, patients with diabetes are more likely to present with acute coronary syndromes (ACSs) than people without diabetes mellitus.[2] In the contemporary INTERHEART study, the presence of diabetes more than doubled the risk of myocardial infarction.[3] Similarly, a large proportion of patients presenting with ACSs have diabetes. In large registries of patients with ACSs—such as the Euro Heart Survey on ACS, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE), and the Global Registry of Acute Coronary Events (GRACE)—the prevalence of known diabetes mellitus has ranged from 23% to 34%.[4–6] Moreover, the Euro Heart Survey on Diabetes and the Heart demonstrated that in patients with ACS, an oral glucose tolerance test reveals impaired glucose tolerance in 32% and diabetes mellitus in 22% of the patients without previously known diabetes.[7] Thus, it can be estimated that more than half of the patients presenting with ACSs have either impaired glucose tolerance or diabetes mellitus.

DIABETES MELLITUS AS A MAJOR RISK FACTOR IN ACUTE CORONARY SYNDROMES

Diabetic patients are more likely to present with atypical symptoms, and in both ST-segment elevation and non–ST-segment elevation myocardial infarction the delay from onset of pain to clinical presentation is longer than in nondiabetic patients.[5,8,9] Moreover, diabetic patients presenting with ACSs are older, more often female, more often obese, and have more comorbidities, specifically hypertension and renal failure.[6,10,11] They also exhibit more complex coronary artery disease than patients without diabetes. In an analysis of the Euro Heart Survey on percutaneous coronary intervention (PCI), the number of patients with severely stenosed segments (>70%) was significantly higher in patients with diabetes compared with patients without ACS.[11] There was also a higher proportion of patients with left main disease and triple vessel disease as well as more type C lesions in patients with versus without diabetes.[11]

Moreover, compared with nondiabetic ACS patients, those with diabetes exhibit increased short-term and long-term mortality.[6,9,11–16] In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry, diabetes independently predicted 2-year mortality (relative risk 1.52, 95% confidence interval [95% CI] 1.38-1.81, $P<0.001$). Subsequently, GRACE reported odds ratios (ORs) for in-hospital death in patients with versus without diabetes of 1.48 (95% CI 1.03-2.31) for ST-segment elevation myocardial infarction (STEMI), 1.14 (95% CI 0.85-1.52) for non–ST-segment elevation myocardial infarction (NSTEMI), and 1.14 (95% CI 1.02-1.95) for unstable angina. Similar results were obtained in a pooled analysis of 62,036 patients of 11 independent ACS trials of the Thrombolysis in Myocardial Infarction (TIMI) study group. In this analysis, diabetes was significantly and independently associated with 30-day and 1-year mortality, both in NSTEMI ACSs and STEMI (hazard ratios [95% CI] 1.65 [1.30-2.10] and 1.12 [1.08-1.38], respectively).[13] The association of diabetes mellitus with poor survival after ACSs is stronger in women than in men.[10]

Hyperglycemia on admission for ACSs also strongly predicts mortality independent of the presence or absence of diabetes mellitus.[17–20] Thorough analyses of the GRACE trial have suggested that fasting glucose levels were better predictors for in-hospital and 6-month survival than the presence or absence of diabetes.[17] Hyperglycemia on admission has been considered to be a strong reflection of an acute stress response.[7] The close relation between glucose metabolism and outcome of ACSs is also reflected by the recent demonstration of an independent association of hemoglobin A1c (HbA1c) with long-term (3.3 ± 1.5 years) mortality after PCI in STEMI.[21]

The association between impaired glucose tolerance and survival after ACSs is less clear. Whereas an earlier study

demonstrated an association between impaired glucose tolerance and poor survival,[22] a more recent analysis of the Euro Heart Survey on diabetes and the heart did not find any significant independent predictive value of impaired glucose tolerance with respect to survival.[23]

In addition to its impact on mortality, the presence of diabetes also increases the risk of heart failure as well as renal failure during the in-hospital phase by approximately twofold in patients presenting with STEMI or NSTEMI ACSs, as shown by the GRACE study,[6] and the risk of bleeding complications by approximately one quarter, as shown by the CRUSADE trial.[24] The risk of recurrent myocardial infarction and heart failure is also increased during long-term follow-up.[14,25,26] Moreover, in a large Danish registry, target lesion revascularization after PCI for ACSs was more often needed in patients with versus without diabetes (adjusted hazard ratio 1.55, 95% CI 1.14-2.11).[14] Even more important, an analysis from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial revealed that the risk of stent thrombosis after placement of a drug-eluting stent in acute myocardial infarction was tripled in patients with diabetes.[27] In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, patients with stent thrombosis more frequently had insulin-requiring diabetes than patients without stent thrombosis, with similar outcomes for drug-eluting and bare metal stents.[28]

BENEFITS OF A PRIMARY INVASIVE STRATEGY

ST-Segment Elevation Myocardial Infarction

In acute myocardial infarction, fibrinolysis compared with conservative treatment reduces the mortality by 18% as shown by a meta-analysis of randomized trials in this setting.[29] In addition to this benefit, coronary reperfusion by primary PCI reduces in-hospital mortality by an additional 37%.[30] Moreover, PCI compared with fibrinolysis reduces the risk of reinfarction and stroke, particularly of hemorrhagic stroke.[31] The initial benefit has been maintained during a long-term follow-up.[31]

The specific role of primary PCI compared with fibrinolysis for myocardial infarction in diabetes mellitus was addressed by a pooled analysis of individual patient data (N = 6315) from 19 trials comparing primary PCI with fibrinolysis.[32] As compared with fibrinolysis, the benefit of primary PCI with respect to 30-day survival was numerically larger in patients with versus without diabetes (**Fig. 22-1**).[32] Nevertheless, a statistically significant *P* value for interaction was not achieved ($P_{int} = .24$). The ORs comparing primary PCI with fibrinolysis with regard to death and recurrent myocardial infarction were similar in patients with and without diabetes (OR [95% CI] 0.52 [0.35-0.77] and 0.51 [0.42-0.61], respectively), whereas those for stroke were numerically more favorable in patients with diabetes (ORs [95% CI] 0.40 [0.16-0.99] and 0.58 [0.39-0.86], respectively), yet without reaching a significant interaction *P* value.[32] Because the incidence of death, recurrent myocardial infarction, and stroke was higher in patients with versus without diabetes irrespective of the treatment modality, similar risk ratios resulted in larger absolute risk reductions. In summary, this meta-analysis demonstrates that primary PCI in patients with diabetes is at least as safe and efficacious as in patients without diabetes and may even confer a larger absolute benefit over fibrinolysis than in patients without diabetes.[32] Nevertheless, the increased mortality associated with diabetes remained.[32] This may be attributed to differences in baseline patient characteristics, but possibly also to less effective microvascular reperfusion. Analyses of the Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial suggested impaired microvascular reperfusion despite similar vessel patency in patients with versus without diabetes.[33] This was evidenced by significantly inferior ST resolution and a significantly lower proportion of patients achieving a myocardial blush grade of 2 or 3 among the diabetes subset of patients.[33]

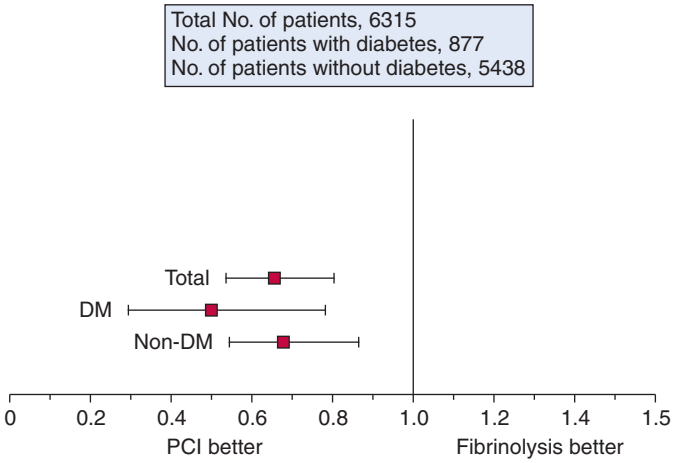


FIGURE 22-1 Adjusted odds ratios and 95% confidence intervals for the risk of 30-day mortality according to the method of reperfusion therapy in patients with and without diabetes. Results from a pooled analysis of individual patient data (N = 6315) from 19 trials.[32] DM = Diabetes mellitus. *(Modified from Timmer JR, Ottervanger JP, de Boer MJ, et al: Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: results from the primary coronary angioplasty vs thrombolysis-2 trial,* Arch Intern Med *167:1353-1359, 2007.)*

Non–ST-Segment Elevation Acute Coronary Syndromes

For high- to intermediate-risk patients with NSTEMI ACSs, current guidelines recommend an invasive strategy that involves coronary angiography and revascularization irrespective of the primary success of medical treatment.[34,35] This recommendation is supported by a number of trials. A meta-analysis published in 2005 concluded that the invasive strategy, although increasing the risk of in-hospital death and myocardial infarction (early hazard), significantly reduced death and myocardial infarction by 18% (95% CI 2%-42%) during the entire follow-up, ranging from 6 months to 2 years in various studies.[36] Some of the studies included in this meta-analysis, however, were not contemporary because of marginal use of stents and low-level use of antiplatelet therapy. Nevertheless, a more recent meta-analysis of eight randomized controlled trials with contemporary management strategies demonstrated that the invasive strategy compared with the conservative strategy significantly reduced the composite of death, myocardial infarction, and rehospitalization because of ACSs at 1 year.[37] Long-term benefits of the invasive strategy over 5 years were addressed by the FIR collaboration, who performed a meta-analysis of individual patient data from three major trials: Fragmin and Fast Revascularization During Instability of Coronary Artery Disease (FRISC II), Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS), and Randomized

trial of a conservative treatment strategy versus an Interventional Treatment strategy in patients with unstable Angina (RITA 3).[38] They found a significant reduction in the 5-year incidence of cardiovascular death and myocardial infarction (hazard ratio [95% CI] 0.81 [0.71-0.93], $P=0.02$), which comprised a significant reduction in the incidence of myocardial infarctions (hazard ratio [95% CI] 0.77 [0.65-0.90], $P=0.01$) and a trend toward decrease in cardiovascular death (hazard ratio [95% CI] 0.83 [0.68-0.01], $P=0.068$).[38] The FIR collaboration also stratified their meta-analysis cohort according to the extent of baseline cardiovascular risk into three groups with low, intermediate, and high risk. As shown in **Figure 22-2**, the benefit of routine invasive strategy versus conservative strategy increased substantially with increasing risk, with an only minor benefit in low-risk patients, but a substantial, more than 10% absolute reduction in the 5-year incidence of death and myocardial infarction in high-risk patients.[38] Among the variables included in this risk stratification, diabetes was the strongest multivariable predictor of risk, with a hazard ratio of 2.06 (95% CI 1.75-2.41).[38]

Extending these findings by specifically addressing the role of diabetes mellitus, a collaborative meta-analysis of nine randomized trials comprising 9904 patients with non–ST-elevation ACSs, of whom 1798 (18.1%) had diabetes, was performed.[39] In this meta-analysis, an invasive strategy was associated with a comparable relative reduction in death, myocardial infarction, or rehospitalization because of ACSs in patients with or without diabetes ($P_{\text{interaction}}=.83$) (**Fig. 22-3**).[39] In diabetic patients, the meta-analysis revealed a significant reduction in the 1-year incidence of nonfatal myocardial infarction by the invasive as compared with the conservative strategy (relative risk [95% CI] 0.71 [0.55-0.92]) and of rehospitalization (relative risk [95% CI] 0.75 [0.61-0.92]).[39] The efficacy of the invasive strategy in reducing recurrent nonfatal myocardial infarction and readmissions for ACSs even appeared to be larger in diabetic patients than in nondiabetic patients. Taken together, the results of this meta-analysis and the results of the FIR collaboration suggest that diabetic patients represent a subset of patients with NSTEMI ACSs who derive particular benefit from an invasive strategy.

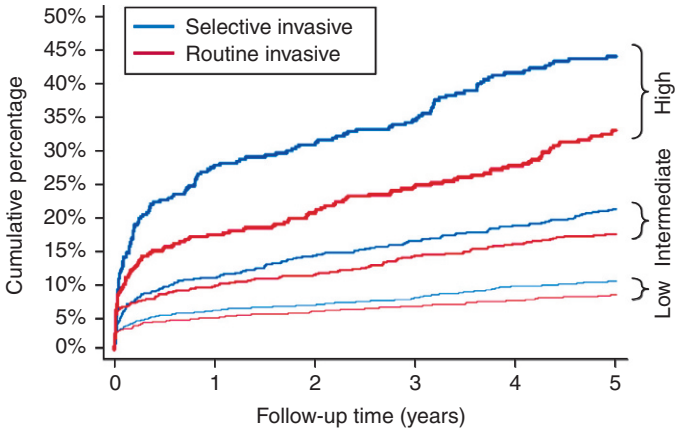


FIGURE 22-2 **Cumulative risk of cardiovascular death or myocardial infarction by risk group in the pooled analysis of patients with non–ST-elevation acute coronary syndromes from FRISC, RITA 3, and ICTUS.**[38] *(Modified from Fox KA, Clayton TC, Damman P, et al: Long-term outcome of a routine versus selective invasive strategy in patients with non–ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data,* J Am Coll Cardiol *55:2435-2445, 2010.)*

TIMING OF INTERVENTION

ST-Segment Elevation Myocardial Infarction

For minimization of myocardial necrosis, reperfusion therapy in acute myocardial infarction should be instituted as soon as possible. Three independent studies have indicated that a delay of up to approximately 2 hours for PCI as compared with immediate fibrinolysis maintains the survival benefit of PCI over fibrinolysis.[30,40,41] It must be kept in mind, however, that the largest benefit of PCI over fibrinolytic therapy was achieved when the delay to PCI was less than an hour.[30] Although fibrinolysis is more effective within the first 1 to 3 hours after onset of symptoms than after larger delays,[42,43] the benefit from PCI as compared with fibrinolysis is largely independent of the time from onset of symptoms to intervention, as shown by meta-analysis of earlier trials.[30] More recently, the Strategic Reperfusion Early after Myocardial Infarction (STREAM) study specifically addressed patients with STEMI who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour.[44] This trial did not show any advantage of fibrinolysis followed by systematic angiography over primary PCI, but a higher risk of stroke with fibrinolysis was reported.[44] The findings of STREAM concur with earlier studies showing no benefit of upstream administration of fibrinolysis[45] and/or abciximab[46] for facilitation of subsequent PCI.

With respect to timing of primary PCI in STEMI, there are no data suggesting that patients with diabetes mellitus need to be managed differently from nondiabetic patients.

Non–ST-Segment Elevation Acute Coronary Syndromes

There is general consensus that among patients with NSTEMI ACSs, those with refractory angina, severe heart failure, life-threatening ventricular arrhythmia, or hemodynamic instability may have an evolving large myocardial infarction and should be taken to coronary angiography and intervention immediately.[34,35]

In most patients presenting with NSTEMI ACSs, however, timing of the intervention is less critical. Nevertheless, intervention should not be intentionally delayed for stabilization and antithrombotic pretreatment (cooling-off strategy).[47,48] Such delay is of no benefit and, specifically, does not reduce the risk of peri-interventional myocardial infarctions.[47] A recent meta-analysis summarized the results of four trials on timing of intervention in NSTEMI ACSs: Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS), Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndrome Randomized for an Immediate or Delayed Intervention (ABOARD), Early or Late Intervention in Unstable Angina (ELISA), and Intracoronary Stenting with Antithrombotic Regimen Cooling-Off (ISAR-COOL).[49] In this meta-analysis, the median time from admission or randomization to coronary angiography ranged from 1.2 to 14 hours in the early and from 21 to 86 hours in the delayed group.[49] The early invasive approach significantly reduced the length of hospital stay by 28% (95% CI 22%-35%, $P<0.001$) and also reduced the incidence of recurrent ischemia (relative risk [95% CI] 0.57 [0.44-0.74]).[49] There also was a trend favoring the early invasive approach toward a lower composite risk of death, myocardial infarction, or stroke (relative risk [95% CI] 0.91 [0.82-0.01]) and lower risk of major bleeding (relative risk [95% CI] 0.78 [0.57-1.07]).[49]

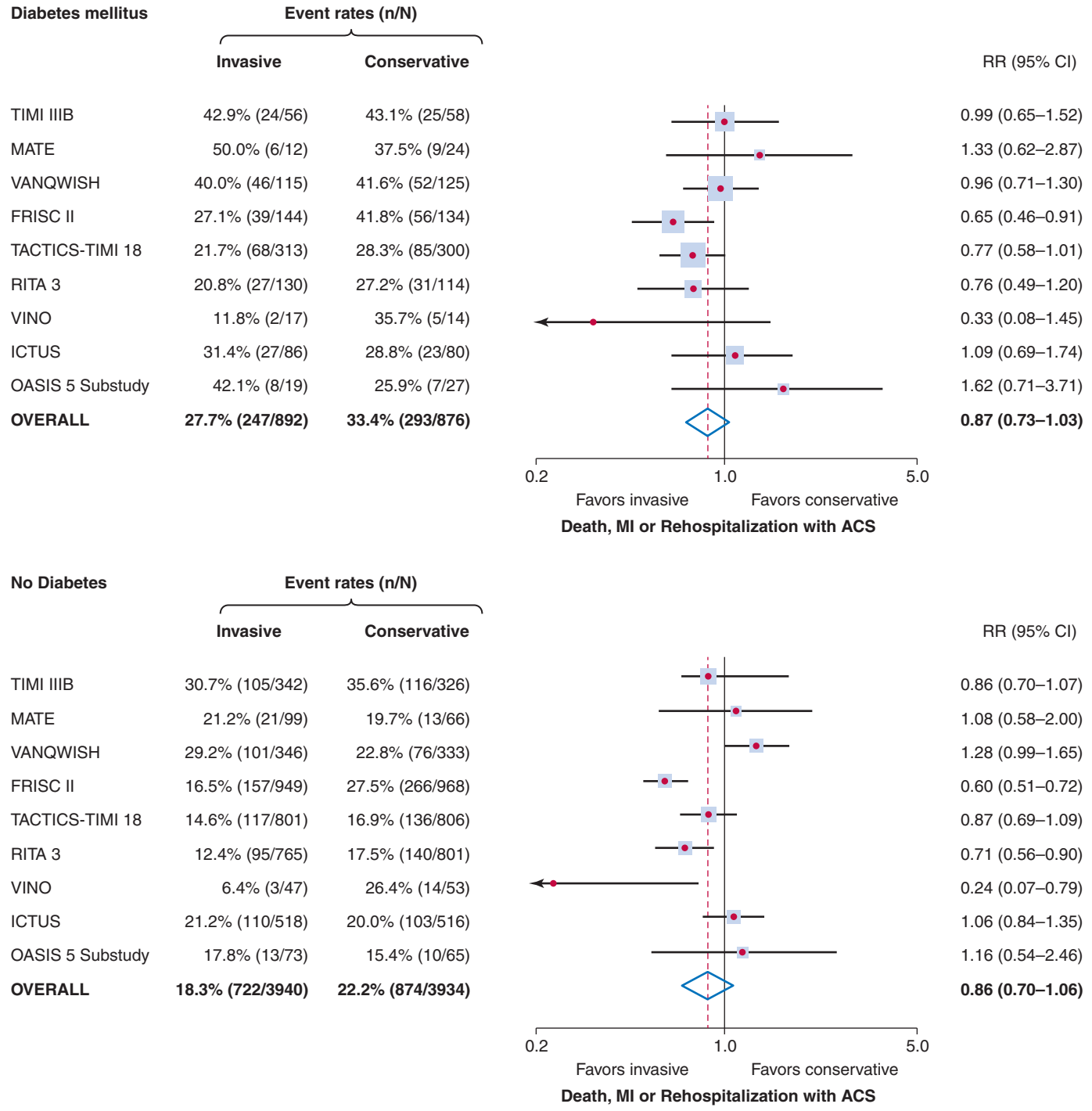


FIGURE 22-3 Benefit of an invasive strategy by diabetes mellitus status. The relative risk (RR) of death, myocardial infarction (MI), or rehospitalization with ACS with an invasive versus conservative treatment strategy stratified by the presence *(top)* or absence *(bottom)* of diabetes mellitus. Results from a meta-analysis of nine randomized trials comprising 9904 patients with non–ST-segment elevation ACSs.[39] Number of patients in denominators reflects those with ascertainment for the composite endpoint. *(Modified from O'Donoghue ML, Vaidya A, Afsal R, et al: An invasive or conservative strategy in patients with diabetes mellitus and non–ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials,* J Am Coll Cardiol *60:106-111, 2012.)*

More detailed insight was obtained from the TIMACS trial, which was the largest study addressing the timing of intervention in NSTEMI ACSs.[50] In TIMACS the cohort was stratified into low- and high-risk subsets according to a GRACE risk score above 140.[50] The GRACE risk score, derived from the GRACE study, is a score to predict mortality in ACSs; it comprises a number of clinical variables including, among others, age, electrocardiographic changes, and cardiac enzymes. In high-risk patients, TIMACS found a significant 38% reduction in death, myocardial infarction, or stroke at 6 months with early (≤24 hours) intervention as compared with delayed intervention (≥36 hours), whereas in the low-risk subsets timing did not matter (**Fig. 22-4**).[50] Based on these findings, it is recommended that patients with high-risk features in general should undergo coronary angiography within 24 hours after admission for a NSTEMI ACS (**Fig. 22-5**).[35] Specifically, this pertains to patients with diabetes mellitus and other high-risk features, even though dedicated studies addressing the timing of intervention in this subset are missing.

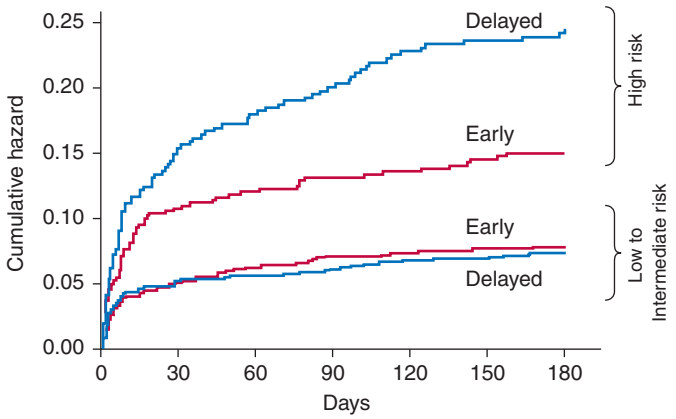


FIGURE 22-4 Kaplan-Meier cumulative risk of death, myocardial infarction, or stroke, stratified according to GRACE risk score at baseline in patients undergoing early versus delayed intervention in the TIMACS trial.[50] Patients who had a GRACE risk score higher than 140 (high risk) benefited more from early intervention than did patients with a score of 140 or lower (low to intermediate risk). *(Modified from Mehta SR, Granger CB, Boden WE, et al: Early versus delayed invasive intervention in acute coronary syndromes,* N Engl J Med *360:2165-2175, 2009.)*

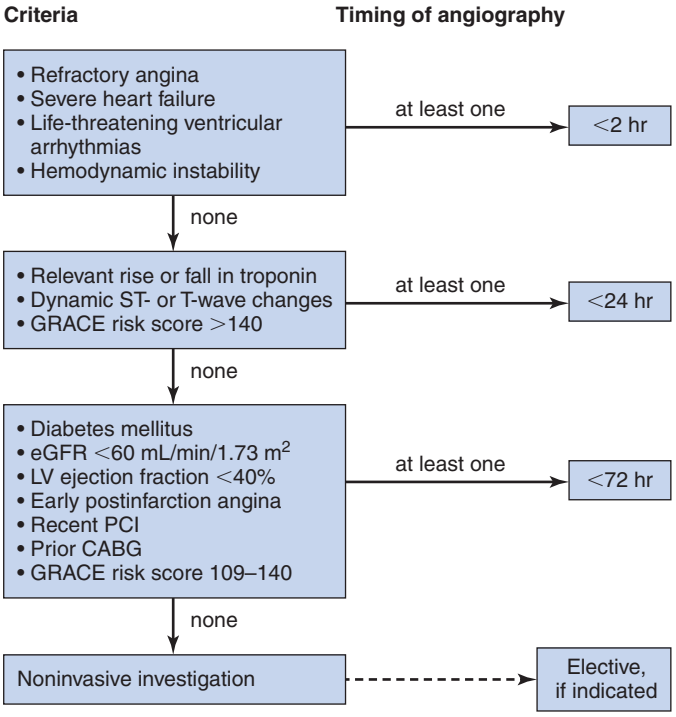


FIGURE 22-5 Suggested algorithm for timing of coronary angiography in non–ST-segment elevation acute coronary syndromes. CABG = coronary artery bypass grafting; eGRF = estimated glomerular filtration rate; LV = left ventricular. *(Modified from Hamm CW, Bassand JP, Agewall S, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society Of Cardiology (ESC),* Eur Heart J *32:2999-3054, 2011.)*

Because the risk of contrast-induced nephropathy is increased in patients with diabetes (OR [95% CI] 1.73 [1.48-2.02]),[51] adequate pretreatment is particularly mandatory in patients with diabetes and impaired renal function before they undergo coronary angiography.[52] Usually this can be achieved by intravenous infusion of isotonic saline for 12 hours before and 24 hours after the intervention.[53–56] In addition, iso-osmolar contrast medium reduces the risk of contrast-induced nephropathy compared with low-osmolar medium.[57] In patients with severely decreased glomerular filtration rate (<30 mL/min/1.73 m^2), prophylactic hemofiltration before PCI followed by hemofiltration for 24 hours after the procedure may be considered.[58] Pretreatment for prevention of contrast-induced nephropathy should not unduly delay coronary intervention for NSTEMI ACSs in diabetic patients with impaired renal function. These patients have a distinctly increased risk of coronary events of more than two-fold compared with patients with diabetes with normal renal function.[59]

Delayed coronary angiography is not required with use of metformin.[34] In contemporary clinical trials[60] and cohort studies[61] of patients with diabetes, the dreaded lactic acidosis was exceedingly rare (five or fewer cases per 100,000 patient-years), and its incidence did not differ between patients on metformin and those on other oral antidiabetic drugs. The most recent ESC guidelines recommend that renal function should be carefully monitored after coronary angiography/PCI in all patients on metformin. In addition, if renal function deteriorates in patients on metformin undergoing coronary angiography/PCI it is recommended to withhold treatment for 48 hours or until renal function has returned to its initial level.[62]

REVASCULARIZATION STRATEGY

ST-Segment Elevation Myocardial Infarction

Acute STEMI is an established prognostic indication for PCI. Compared with PCI, coronary artery bypass grafting (CABG) delays reperfusion and is associated with a high perioperative risk.[63,64] Nevertheless, CABG may be indicated as the primary reperfusion strategy for complex coronary anatomy, particularly when the culprit lesion cannot be identified with certainty. Also, CABG may be needed as treatment for failed PCI or as part of repair of mechanical complications after infarction. In the Primary Angioplasty in Myocardial Infarction (PAMI-2) study, 5.3% of the patients underwent CABG as the primary reperfusion strategy, and 6.1% as a secondary intervention.[65] More recently in the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS), the corresponding percentages for CABG were substantially lower, 0.65% and 4.86%, respectively.[66] Because of more complex coronary disease, diabetic patients in PAMI-2 were more likely to undergo in-hospital cardiac surgery after STEMI than patients without diabetes (OR [95% CI] 1.96 [1.21-3.10]). In PAMI-2, early and late survival free of reinfarction adjusted for baseline risk factors were similar in patients undergoing versus patients not undergoing in-hospital cardiac surgery.[65] Nevertheless, early complications, such as bleeding and recurrent ischemia, were frequent in surgical patients.[65] TAPAS yielded similar results: Despite a higher incidence of surgical complications, surgical management during the acute and subacute phase was associated with excellent 30-day and 1-year survival.[66]

Non–ST-Segment Elevation Acute Coronary Syndromes

In NSTEMI ACSs, revascularization by CABG carries a substantially increased risk,[67,68] particularly if myocardial marker proteins are elevated.[69] Treatment of the culprit lesion in NSTEMI is therefore generally considered to be the domain of PCI.

Yet, dedicated studies addressing the optimal revascularization strategy in NSTEMI ACSs are lacking. Thus, treatment decisions need to be based on individual considerations, taking into account the location of the culprit lesion and the amount of the jeopardized downstream myocardium, the ischemic damage that has already occurred, the extent of coronary artery disease outside the culprit lesion, and the specific risks of PCI and CABG in this setting. Depending on the culprit lesion and the extent of myocardial ischemia, the treatment strategy needs to follow the same principles as in STEMI. In most patients, however, the criteria derived from studies in stable angina may guide the choice of revascularization modality, as recommended by contemporary guidelines.[34,35]

Whereas single-vessel disease may be safely and efficiently treated with PCI,[34] decision making is more complex in multivessel disease. The recently published findings of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial compared the 5-year outcome of CABG with that of PCI in diabetic patients under optimal medical therapy.[70] The study enrolled 1900 patients, of whom 31% presented with a recent ACS. The primary outcome, the 5-year composite incidence of death from any cause, nonfatal myocardial infarction, or nonfatal stroke, occurred more frequently in the PCI group ($P=0.05$) with rates of 26.6% after PCI and 18.7% after CABG (**Fig. 22-6**).[70] There was a substantial 5-year survival benefit of CABG (10.9% versus 16.3%; $P=0.049$), and the 5-year incidence of myocardial infarction was also lower after CABG than after PCI (6.0% versus 13.9%; $P<0.01$) (see **Fig. 22-6**).[70] The benefit of CABG was similar in two-vessel and three-vessel disease (**Fig. 22-7**).[70] The authors also quantified the extent and complexity of coronary artery disease by the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, which accounts for the number of lesions, their location, and the angiographic characteristics associated with poor outcome. A subgroup analysis was performed according to low (≤22), intermediate (23 to 32), and high (≥33) SYNTAX scores. These thresholds were derived from the previously published SYNTAX trial.[71] In the low range of SYNTAX scores, the hazard ratio comparing CABG with PCI was close to unity and statistically insignificant, whereas at SYNTAX scores of 23 and above, a substantial and statistically significant benefit of CABG was found (see **Fig. 22-7**).[70] These findings are, however, difficult to interpret because the *P* value for interaction did not reach statistical significance ($P_{int}=.485$).[70]

Additional evidence is presented by the SYNTAX trial, which compared CABG with PCI with the paclitaxel-eluting stent in patients with three-vessel disease or left main coronary artery disease with or without distal coronary artery stenoses. In SYNTAX, 1800 patients underwent randomization; 28% presented with unstable angina.[71] Results from the diabetic subgroup, comprising 453 randomized patients, were published recently.[72] Among diabetic patients, the 5-year incidence of the primary endpoint, the composite of all-cause death, myocardial infarction, stroke, and repeat revascularization, was significantly lower after CABG than after PCI (29.0% versus 46.5%; $P<0.001$), which was largely driven by a significant difference in the need for repeat revascularization (16.4 versus 35.3%; $P<0.001$).[72] Consistent with FREEDOM, there also was a trend toward better survival after CABG compared with PCI (mortality 12.9% versus 19.5%; $P=0.065$), which included a significant difference in the incidence of cardiac death (6.5% versus 12.7%; $P=0.034$).[72] The difference in survival between CABG and PCI was largely the result of a high cardiac mortality in insulin-treated patients undergoing PCI. At low SYNTAX scores, the 5-year incidence of death, myocardial infarction, and stroke was similar after CABG or PCI; yet the need for repeat revascularization remained higher after PCI than after CABG even at low SYNTAX scores (**Fig. 22-8**).[72]

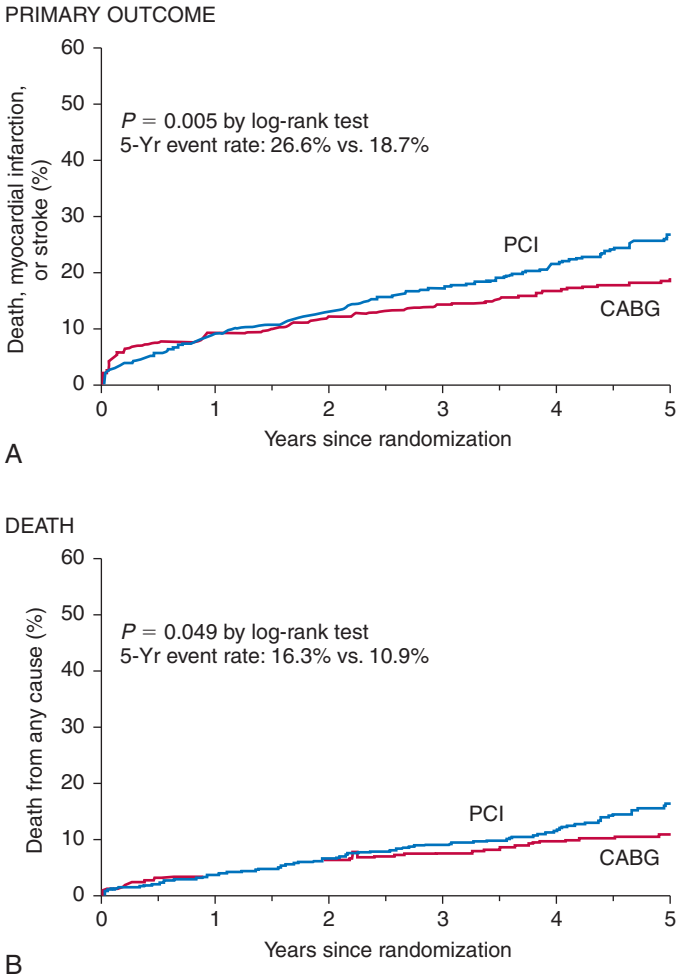


FIGURE 22-6 Kaplan-Meier estimates of the composite primary outcome and death in the FREEDOM trial comparing PCI with CABG in diabetic patients with coronary multivessel disease.[70] Shown are rates of the composite primary outcome of death, myocardial infarction, or stroke **(A)** and death from any cause **(B)** truncated at 5 years after randomization. The *P* value was calculated by means of the log-rank test on the basis of all available follow-up data. *(Modified from Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes,* N Engl J Med *367:2375-2384, 2012.)*

Although subgroup analyses for patients with ACSs from FREEDOM or SYNTAX have not been reported yet, the available 5-year data strongly suggest that in diabetic patients presenting with ACSs, CABG is the treatment of choice for complex multivessel coronary disease.[62] In less complex cases, PCI may be considered, too.

PROCEDURAL ASPECTS OF PERCUTANEOUS CORONARY INTERVENTION AND CORONARY ARTERY BYPASS GRAFTING

Completeness of Revascularization

Several independent studies have demonstrated that incomplete as compared with complete revascularization

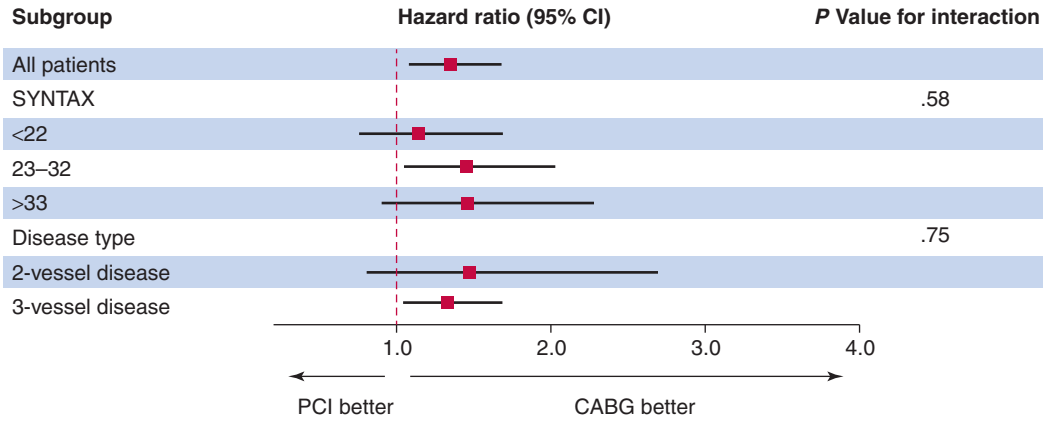


FIGURE 22-7 Primary composite outcome, according to subgroup of the FREEDOM trial comparing PCI with CABG in diabetic patients with coronary multivessel disease.[70] Subgroup analyses were performed with the use of Cox proportional-hazards regression. Five-year composite event rates for death, myocardial infarction, or stroke are shown. *(Modified from Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes,* N Engl J Med *367:2375-2384, 2012.)*

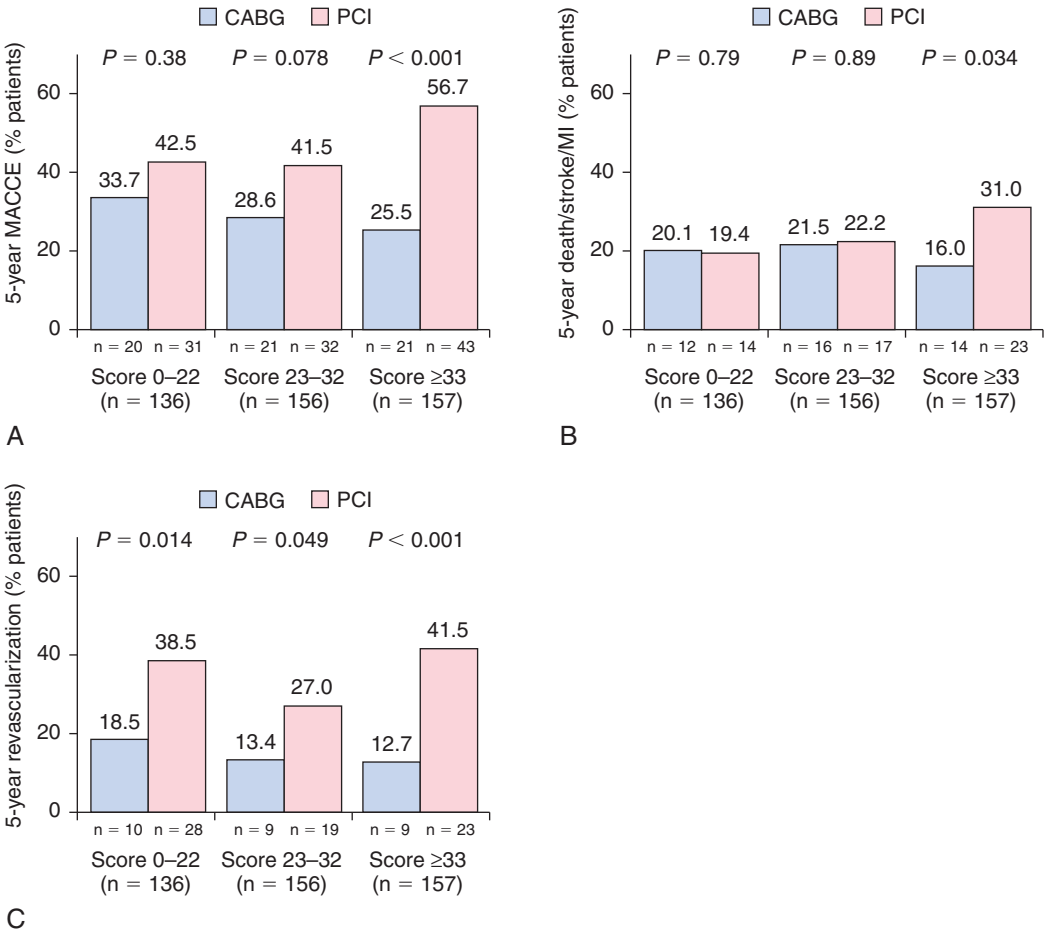


FIGURE 22-8 Five-year outcomes for diabetic patients and nondiabetic patients according to anatomic lesion complexity, as measured by the SYNTAX score. Results from the SYNTAX trial comparing CABG with PCI in patients with three-vessel disease or left main coronary artery disease with or without distal coronary artery stenosis. Shown are binary event rates of **(A)** major adverse cardiac or cerebrovascular events (MACCE); **(B)** the composite endpoint of all-cause death, stroke, and myocardial infarction; and **(C)** repeat revascularization in diabetic patients. Rates are separated according to SYNTAX score tertiles, indicating low (0 to 22), intermediate (23 to 32), and high (≥33) anatomic lesion complexity. CABG, blue bars; PCI, pink bars. *(Modified from Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the syntax trial,* Eur J Cardiothorac Surg *43:1006-1013, 2013.)*

is associated with inferior survival, both after PCI[73] and after CABG.[74,75] In a recent subanalysis of the SYNTAX trial, the incompleteness of revascularization after PCI was quantitated by the residual SYNTAX score—the SYNTAX score calculated after PCI. A progressively higher residual SYNTAX score was shown to be associated with increased 5-year mortality. Patients with complete revascularization (and therefore low residual SYNTAX scores) had a 5-year mortality of 8.5%, whereas in those with a residual SYNTAX score above 8, 5-year mortality rose to 35.3% ($P < 0.01$). These

results were consistent across various subsets including patients with diabetes.

Specifically addressing patients with diabetes, an analysis from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study revealed that diabetic patients with less complete revascularization had more long-term cardiovascular events than those with more complete revascularization, irrespective of whether they had been treated with PCI or CABG.[76] Earlier, the Bypass Angioplasty Revascularization Investigation (BARI) also suggested the relevance of complete revascularization in patients with diabetes. In BARI, the more complete revascularization of diabetic patients by CABG, especially when an arterial conduit was used for the LAD, as compared with plain balloon angioplasty[77] was considered to be a major cause for the survival benefit of CABG seen in this trial (see also **Chapter 18**).[78]

Staged Revascularization for Multivessel Coronary Disease

Given the importance of complete revascularization, there is continued debate about whether this should be achieved during the same procedure as for the culprit lesion (single-step approach) or whether a superior method is a staged procedure that involves initial treatment of the culprit lesion and subsequent treatment of the other lesions after further stabilization. Dedicated adequately powered randomized studies comparing the single-step approach with the staged approach are currently missing. A relevant retrospective analysis in this respect is based on the HORIZONS-AMI trial.[79] In a factorial design, this trial primarily compared bivalirudin versus heparin plus a glycoprotein (GP) IIB/IIIa inhibitor[79] and paclitaxel-eluting stents versus bare metal stents[80] in patients undergoing PCI for STEMI. In this trial, 668 patients underwent PCI of culprit and nonculprit lesions for multivessel disease.[81] Staged PCI was associated with significantly lower 1-year mortality than single-step PCI (9.2% versus 3.2%; $P<0.001$).[81] Even after adjustment for differences in baseline characteristics, the difference in all-cause mortality favoring staged PCI over single-step PCI remained statistically significant at 30 days and at 1 year.[81] This analysis did not address the role of diabetes mellitus, specifically.

In a network meta-analysis of 15 studies, long-term mortality after staged PCI was significantly lower than after single-step multivessel PCI (OR 0.34 [95% CI 0.20-0.58]).[82] Staged PCI also conferred a significant benefit compared with single-step culprit-only PCI (OR 0.56 [95% CI 0.34-0.87]).[82] A more recent small (N = 465) randomized study found a benefit of single-step multivessel PCI over culprit-only PCI, but did not address staged multivessel PCI.[83] Therefore in the absence of definite proof, staged PCI may still be considered to be a reasonable approach for unselected patient cohorts with STEMI. However, to what extent patients with STEMI and cardiogenic shock may benefit from single-step multivessel PCI is still a matter of debate.

The limited clinical experience with respect to the comparison of staged versus single-step PCI for multivessel disease in ACSs is derived from mixed populations comprising patients both with and without diabetes. There is, however, no indication that patients with diabetes are in special need of single-step multivessel PCI in this setting.

Percutaneous Coronary Intervention with Drug-Eluting Stents

Dedicated clinical studies on the optimal choice of stent type in diabetic patients undergoing PCI for ACSs are missing. There is, however, extensive literature on the choice of stent type in myocardial infarction (irrespective of the presence or absence of diabetes) and in patients with diabetes (irrespective of the presence or absence of ACSs). As discussed in **Chapter 17**, drug-eluting stents compared with bare metal stents substantially reduce the need for target lesion reinterventions in patients with diabetes mellitus. The absolute reduction in the risk of target lesion revascularization by drug-eluting stents is even larger in patients with diabetes than in patients without diabetes, although relative risk reductions are similar. Moreover, even in patients with diabetes, drug-eluting stents are at least as safe as bare metal stents, provided that adequate dual antiplatelet therapy is administered.

Concerning the choice of stent type in ACSs, it is now generally accepted that in the absence of contraindications to extended dual antiplatelet therapy, drug-eluting stents are the treatment of choice for PCI in this setting.[34,84] This concept is based on a number of studies that showed increased efficacy of drug-eluting stents in acute myocardial infarction without any safety issue, as summarized by two independent meta-analyses.[85,86] The largest randomized study in this setting is HORIZONS-AMI.[80] Notably, HORIZONS-AMI identified three independent risk factors for restenosis after PCI in STEMI: insulin-treated diabetes mellitus (hazard ratio 3.12 [95% CI 1.23-7.87]), baseline reference vessel diameter 3.0 mm or smaller (hazard ratio 2.89 [95% CI 1.56-5.34]), and total lesion length of 30 mm or greater (hazard ratio 2.49 [95% CI 1.33-4.68]).[87] Underscoring the particular benefit of drug-eluting stents in patients with diabetes with STEMI, the reduction in restenosis by the paclitaxel-eluting stent compared with the bare metal stent increased substantially with increasing number of risk factors for restenosis (**Fig. 22-9**).[87] There was no safety issue associated with the paclitaxel-eluting stent. On the contrary, in patients with two or more risk factors for restenosis, there was trend toward lower 12-month cardiac mortality after paclitaxel-eluting stents compared with bare metal stents (2.4% versus 6.2%; $P=0.08$).[87]

SUMMARY

More than half of all patients with ACSs have either diabetes mellitus or impaired glucose tolerance. Patients with diabetes are more likely to present with atypical symptoms, and in both STEMI and NSTEMI, the delay from onset of pain to clinical presentation is longer than in patients without diabetes. Because of more frequent comorbidities and more complex coronary artery disease, patients with diabetes exhibit an increased short-term and long-term mortality after ACS compared with patients without diabetes. In addition to its impact on mortality, the presence of diabetes also increases the risk of heart failure and renal failure during the in-hospital phase, as well as the risk of bleeding complications.

In STEMI, primary PCI is at least as safe and efficacious in patients with diabetes as in patients without diabetes and may even confer a larger absolute benefit over fibrinolysis. Primary PCI must be performed as soon as possible, preferably within the first hour after first medical contact. In any

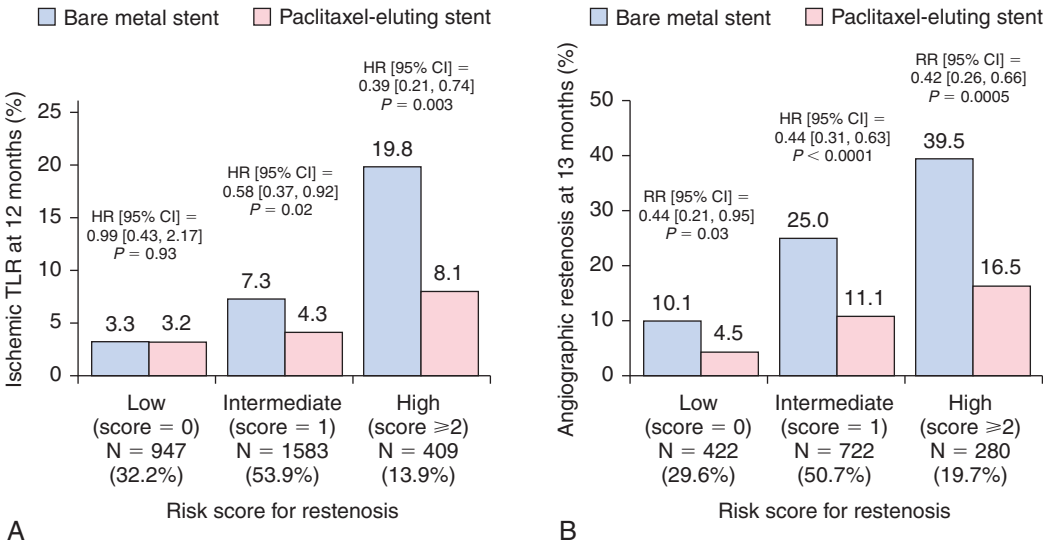


FIGURE 22-9 Rates of 12-month ischemic target lesion revascularization (TLR; A) and 13-month angiographic restenosis (B) in patients randomly allocated to paclitaxel-eluting stents (pink bars) or to bare metal stents (blue bars) according to the risk strata for restenosis. Results from the HORIZONS-AMI trial comparing paclitaxel-eluting stents with bare metal stents in patients undergoing PCI for ST-elevation myocardial infarction. RR = relative risk. *(Modified from Stone GW, Parise H, Witzenbichler B, et al. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial,* J Am Coll Cardiol *56:1597-1604, 2010.)*

case, the delay for PCI compared with fibrinolysis may not exceed 2 hours to maintain the survival benefit of PCI over fibrinolysis. In multivessel disease, staged revascularization is the preferred approach in the absence of cardiogenic shock, based on currently available inconclusive evidence. Although PCI is the primary treatment of choice, CABG may be indicated for complex coronary anatomy.

In NSTEMI ACSs with high to intermediate risk, an invasive strategy that involves coronary angiography and revascularization irrespective of the primary success of medical treatment reduces the long-term risk of death and myocardial infarction. Patients with diabetes represent a subset of patients with NSTEMI ACSs who derive particular benefit from an invasive strategy. Although timing of the intervention is less critical in NSTEMI ACSs than in STEMI, intervention should not be intentionally delayed for stabilization and antithrombotic pretreatment (cooling-off strategy). In general, patients with high-risk features should undergo coronary angiography within 24 hours after admission with a NSTEMI ACS. Metformin does not require delayed coronary angiography. Yet pretreatment for prevention of contrast-induced nephropathy should be considered in patients with diabetes and impaired renal function unless the clinical setting does not allow for such delay.

Dedicated studies addressing the optimal revascularization strategy in NSTEMI ACSs are lacking. Thus, treatment decisions need to be based on individual considerations, taking into account the location of the culprit lesion and the amount of the jeopardized downstream myocardium, the ischemic damage that has already occurred, the extent of coronary artery disease outside the culprit lesion, and the specific risks of PCI and CABG in this setting. In general, the primary treatment of the culprit lesion will be PCI. It has to be considered, however, that in multivessel coronary disease, patients with diabetes are more likely to derive a larger benefit from CABG as compared with PCI than are patients without diabetes. Irrespective of the treatment modality, complete revascularization should be achieved. If the choice is PCI, drug-eluting stents are preferred in both NSTEMI ACSs and STEMI.

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PART V

HEART FAILURE IN DIABETES

23 Epidemiology of Heart Failure in Diabetes

David Aguilar

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Multiple epidemiologic studies have demonstrated that diabetes mellitus (DM) is associated with increased risk for the development of heart failure (HF). The mechanisms contributing to this greater risk are likely multifactorial and include the often accelerated comorbid conditions such as obesity, hypertension, and coronary artery disease (CAD). In addition, diabetes may contribute to cardiac dysfunction through other pathways related to insulin resistance, including lipotoxicity, abnormal calcium handling, mitochondrial dysfunction, increased reactive oxygen species, abnormalities in autophagy, and changes in adipokines (see also **Chapter 24**). It is important to note that the coexistence of diabetes and HF in a patient is associated with increased morbidity and mortality. This chapter reviews the epidemiology of diabetes and HF.

ASSOCIATION OF DIABETES AND INCIDENT HEART FAILURE

Multiple epidemiologic studies have demonstrated that diabetes increases the risk for the development of HF (**Table 23-1**). In the first 20 years of follow-up in the Framingham Heart Study, diabetes was associated with an almost twofold increased risk of HF in men and a fourfold increased risk in women independent of other risk factors (age, systolic blood pressure, tobacco use, cholesterol, and left ventricular (LV) hypertrophy).[1] Multivariable analyses revealed that diabetes had a high population attributable risk for HF in the Framingham Heart Study, accounting for 6% of cases in men and 12% in women.[2] In the Multi-Ethnic Study of Atherosclerosis (MESA) study of 6814 individuals free of symptomatic cardiovascular disease (CVD) at baseline, diabetes was associated with an almost twofold increased risk for the development of HF, independent of other established risk factors, including baseline LV function (hazard ratio [HR] 1.99, 95% confidence interval [CI] 1.08-3.68).[3] In the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study, the multivariable adjusted relative risk associated with diabetes for the development of HF was 1.85 (95% CI 1.51-2.28; $P < 0.001$), and the population attributable risk for diabetes was 3.1%.[4] Several other epidemiologic studies have also confirmed that DM is associated with a 2-fold to 3.5-fold increased risk for the development of incident HF compared with the risk in people without diabetes in the general population.[5–7]

Other studies in populations with greater baseline risk of developing HF have also demonstrated that diabetes is independently associated with incident HF. For example, in the Cardiovascular Health Study of people 65 years of age or older, the multivariable adjusted relative risk of HF in people with diabetes compared with those without diabetes was 1.74 (95% CI 1.38-2.19).[8] In the Cardiovascular Health Study, the incidence rates of HF in men and women with diabetes were 44.6 and 32.5/1000 person-years, respectively, and were markedly greater than in those without diabetes (see **Table 23-1**).[8] In patients with established CAD, diabetes also remains a powerful risk factor for incident HF. In the Heart and Soul Study of 839 individuals with stable CAD, individuals with diabetes had a threefold increased risk of HF compared with those without diabetes (adjusted HR 3.34, 95% CI 1.65-6.76).[9] The incidence rate of HF in the Heart and Soul Study was 36.6/1000 person-years and 17.9/1000 person-years in individuals with and without diabetes, respectively.[9] Diabetes was associated with a more-than-doubled risk of development of HF in patients with stable CAD enrolled in the PEACE clinical trial (HR 2.16, 95% CI 1.67-2.79).[10] Finally, among 2391 women with established CAD who were free of HF at baseline and who were enrolled in the Heart and Estrogen/Progestin Replacement Study (HERS), diabetes was the strongest risk factor for the development of HF (adjusted HR 3.1, 95% CI 2.3-4.2).[11]

TABLE 23-1 Incidence of Heart Failure (HF) in Individuals With and Without Diabetes in Select Epidemiologic Studies

STUDY	SAMPLE	FOLLOW-UP (TIME)	HF EVENTS (INCIDENCE)	RISK FOR HF COMPARED WITH RISK IN PATIENTS WITHOUT DIABETES (ADJUSTED)	POPULATION ATTRIBUTABLE FRACTION
Framingham[1]	5209 individuals	20 yr	DM (men): 7.6/1000 person-yr (age-adjusted) No DM (men): 3.5/1000 person-yr (age-adjusted) DM (women): 11.4/1000 person-yr (age-adjusted) No DM (women): 2.2/1000 person-yr (age-adjusted)	RR (men): 1.82 RR (women): 3.75	Men 7.7% Women 18.6%
Cardiovascular Health Study[8]	5888 individuals older than 65 yr	Average 5.5 yr	DM (men): 44.6/1000 person-yr No DM (men): 22.9/100 person-yr DM (women): 32.5/1000 person-yr No DM (women): 12.1/1000 person-yr	RR: 1.74 (95% CI 1.38-2.19)	8.3%
Heart and Soul Study[9]	839 participants with stable CAD	Mean 4.1 years	DM: 36.6/1000 person-yr No DM: 17.9/1000 person-yr	HR: 3.34 (95% CI 1.65-6.76).	N/A

CI = Confidence interval; HR = hazard ratio; RR = relative risk.

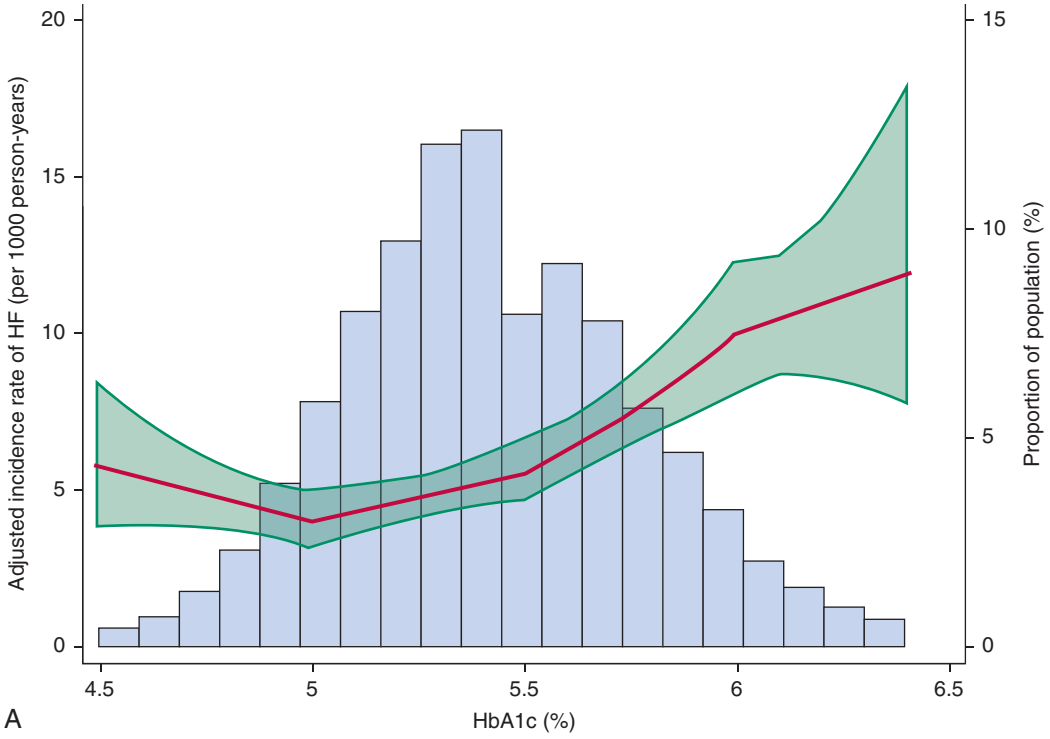


FIGURE 23-1 Incident rates of HF according to HbA1c. The graph shows incidence rates (per 1000 person-years) and 95% CI (shaded area) of HF with spline terms of A1c (knots at 5.0%, 5.5%, and 6.0%). *(Modified from Matsushita K, Blecker S, Pazin-Filho A, et al: The association of hemoglobin a1c with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities study,* Diabetes *59:2020-2026, 2010.)*

In addition to overt diabetes, epidemiologic studies have also demonstrated that milder abnormalities of glucose regulation (below the diagnostic threshold for diabetes) are associated with increased rates of HF. In a community-based, observational cohort of 1187 elderly men without congestive heart failure (CHF) and valvular disease at baseline, parameters of insulin resistance (clamp glucose disposal rate and fasting proinsulin level) predicted CHF incidence independently of established risk factors including clinical diabetes.[12] Similarly, in participants without diabetes or HF at baseline in the Atherosclerosis Risk in Communities (ARIC) study, incident HF rates increased in a stepwise manner with increasing hemoglobin A1c (HbA1c) when compared with the reference group (HbA1c 5.0% to 5.4%) (**Fig. 23-1**).[13]

Risk factors for incident HF in patients with diabetes are similar to those in individuals without diabetes (see also **Chapter 25**). Cohort studies of individuals with diabetes have shown that risk factors for the development of HF include older age, the presence of ischemic heart disease and CAD, peripheral vascular disease, nephropathy and renal insufficiency, metabolic complications of diabetes, retinopathy, diabetes duration, obesity, and hypertension.[7,11,14] In addition, multiple studies have demonstrated that worsened glycemic control is associated with greater risk for the development of HF in individuals with diabetes. Several

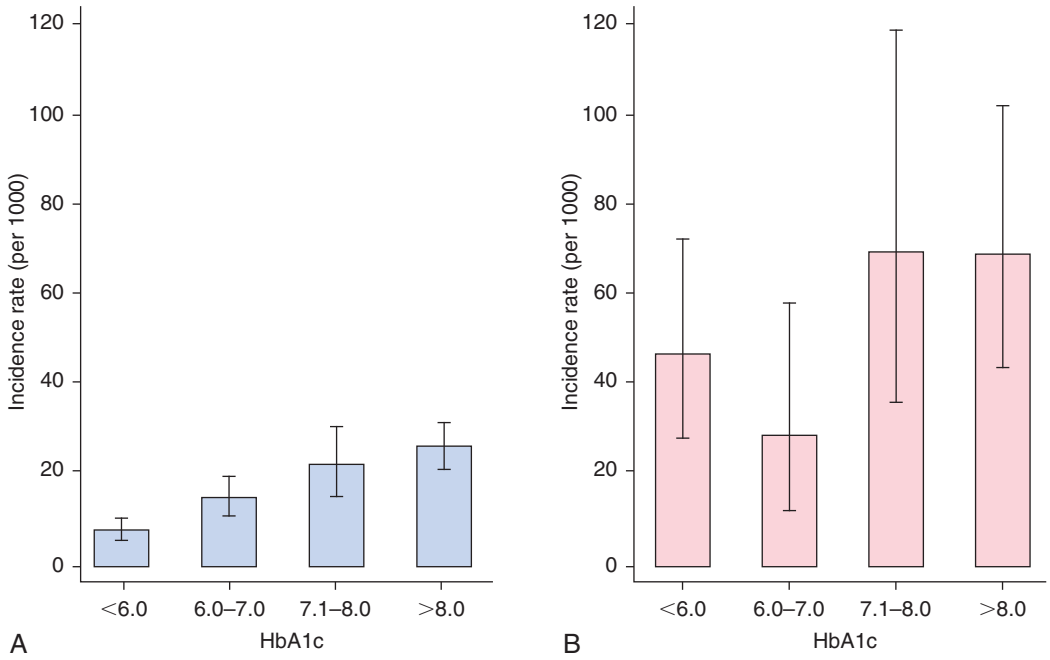


FIGURE 23-2 Crude incidence rates (95% CI) of HF in diabetic participants in the ARIC study by baseline HbA1c categories and coronary heart disease (CHD) status at baseline (**A,** without CHD; **B,** with CHD). *(Modified from Pazin-Filho A, Kottgen A, Bertoni AG, et al: HbA1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study,* Diabetologia *51:2197-2204, 2008.)*

TABLE 23-2 Heart Failure (HF) Event Rate in Selected Clinical Trials of Individuals with Diabetes

TRIAL	POPULATION	MEAN FOLLOW-UP (YR)	NUMBER OF HF EVENTS/ TOTAL SAMPLE (%)	HF EVENT RATE/1000 PERSON-YR
UKPDS[20]	Newly diagnosed T2DM	10	116/3867 (2.9%)	3.0
ACCORD[27]	T2DM + CVD or CV risk factors	3.5	276/10,251 (2.7%)	7.7
BARI 2D[28]	T2DM + stable CAD	5.3	466/2191 (21.3%)	40.1
TREAT[29]	T2DM + CKD + anemia	2.4	434/4038 (10.7%)	44.3

Approximate HF event rates were calculated by dividing the number of events in each trial group by the corresponding number of person-years. ACCORD = Action to Control Cardiovascular Risk in Diabetes; BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; CKD = chronic kidney disease; CV = cardiovascular; T2DM = type 2 diabetes mellitus; TREAT = Trial to Reduce Cardiovascular Events with Aranesp Therapy; UKPDS = United Kingdom Prospective Diabetes Study.

studies have demonstrated that for each 1% increase in HbA1c in individuals with diabetes, the risk of incident HF increases by 8% to 36%.[9,15–17] The relationship between HbA1c and incident HF in a community-based study of diabetic individuals with and without baseline coronary heart disease is shown in **Figure 23-2**.[16]

Specific glucose-lowering therapies have also been associated with incident HF. Observational studies have demonstrated that insulin use at baseline is associated with increased rates of HF in diabetic individuals,[7,18] but it remains unclear whether insulin use is a marker of diabetes duration and severity or contributing to cardiac dysfunction. Long-term follow-up of randomized, controlled clinical trials that have prospectively studied insulin use have not confirmed greater rates of HF associated with insulin,[19,20] suggesting that insulin is more likely a marker for diabetes duration and severity rather than a contributor to greater rates of HF. Thiazolidinediones (TZDs) have been associated with fluid retention and increased rates of HF in randomized controlled trials.[21–24] Although the exact mechanisms of the increased HF events with TZDs are not known, the predominant proposed mechanism relates to TZD-associated volume expansion caused by increased renal sodium reabsorption[25] rather than a direct effect on myocardial structure and function.[26]

As expected, rates of incident HF in diabetic patients vary depending on concomitant HF risk factors present. The heterogeneity of HF event rates for several diabetic clinical trials is demonstrated in **Table 23-2**. In the United Kingdom Prospective Diabetes Study (UKPDS), which enrolled individuals with newly diagnosed diabetes (of whom only 2% had macrovascular disease at baseline), the HF event rate was 3.0/1000 person-years.[20] In diabetic participants with multiple cardiovascular (CV) risk factors or established CAD such as those enrolled in the ACCORD trial, the HF event rate was 7.7/1000 person-years.[27] In comparison, in BARI 2D, a trial of patients with type 2 diabetes and obstructive CAD that was deemed suitable for revascularization, the HF event rate was 40.1/1000 person-years.[28] Finally, in patients with chronic kidney disease, anemia, and type 2 diabetes enrolled in the TREAT study, the HF event rate was 44.3/1000 person-years.[29]

PREVALENCE OF HEART FAILURE AND CARDIAC DYSFUNCTION IN PEOPLE WITH DIABETES

The prevalence of HF is approximately 2% in adults older than 20 years in the general population, and HF prevalence increases with age such that HF prevalence is estimated to

be 4.5% in women and 7.8% in men who are 60 to 79 years old.[30] Estimated HF prevalence in patients with type 2 diabetes is greater than in the general population, and estimates have ranged from approximately 12% in the general population[31,32] to 20% to 28% in diabetic individuals aged 60 years or older (**Fig. 23-3**).[14,31,33] The prevalence of HF is also increased in patients with glycemic abnormalities below the threshold for diabetes as compared with individuals with normal glucose tolerance (see **Fig. 23-3**).[31]

In addition to overt clinical HF, asymptomatic LV dysfunction and abnormalities of cardiac structure and function are also more commonly present in patients with diabetes than in those without diabetes. In the general adult population, the prevalence of asymptomatic LV dysfunction is approximately 3% to 6%.[34] In patients with diabetes, the prevalence of asymptomatic LV dysfunction in the Framingham Heart Study (left ventricular ejection fraction [LVEF] <50%) was 7%.[35] In a study of individuals with diabetes and hypertension, the prevalence of mild (LVEF 41% to 54%) and severe asymptomatic LV dysfunction (LVEF ≤40%) was 12.1% and 5.1%, respectively.[36]

Subclinical abnormalities of cardiac structure and diastolic function are also commonly present in patients with diabetes (i.e., diabetic cardiomyopathy; see also **Chapter 24**). These structural changes include diabetes-associated increases in LV mass, relative wall thickness, and left atrial size.[37–40] In a large study of more than 12,000 diabetic patients without existing clinical HF, preclinical diastolic dysfunction, defined as an E/e′ (passive transmitral LV inflow velocity to tissue Doppler imaging velocity of the medial mitral annulus during passive filling ratio) greater than 15, was present in approximately 23% of patients.[41] It is important to note that the presence of preclinical diastolic dysfunction was independently predictive of subsequent HF (HR 1.67, 95% CI 1.20-2.33, $P = 0.003$) and death (HR 2.14, 95% CI 1.36-3.36) (**Fig. 23-4**).[41]

PREVALENCE OF DIABETES IN PATIENTS WITH HEART FAILURE

In individuals with symptomatic HF, population studies have demonstrated that the prevalence of diabetes varies from 12% to 33% depending on the population studied.[42,43] For example, in Olmsted County, Minnesota, approximately 20% of individuals with a new diagnosis of HF had previously recognized diabetes.[44] In Olmsted County the prevalence of

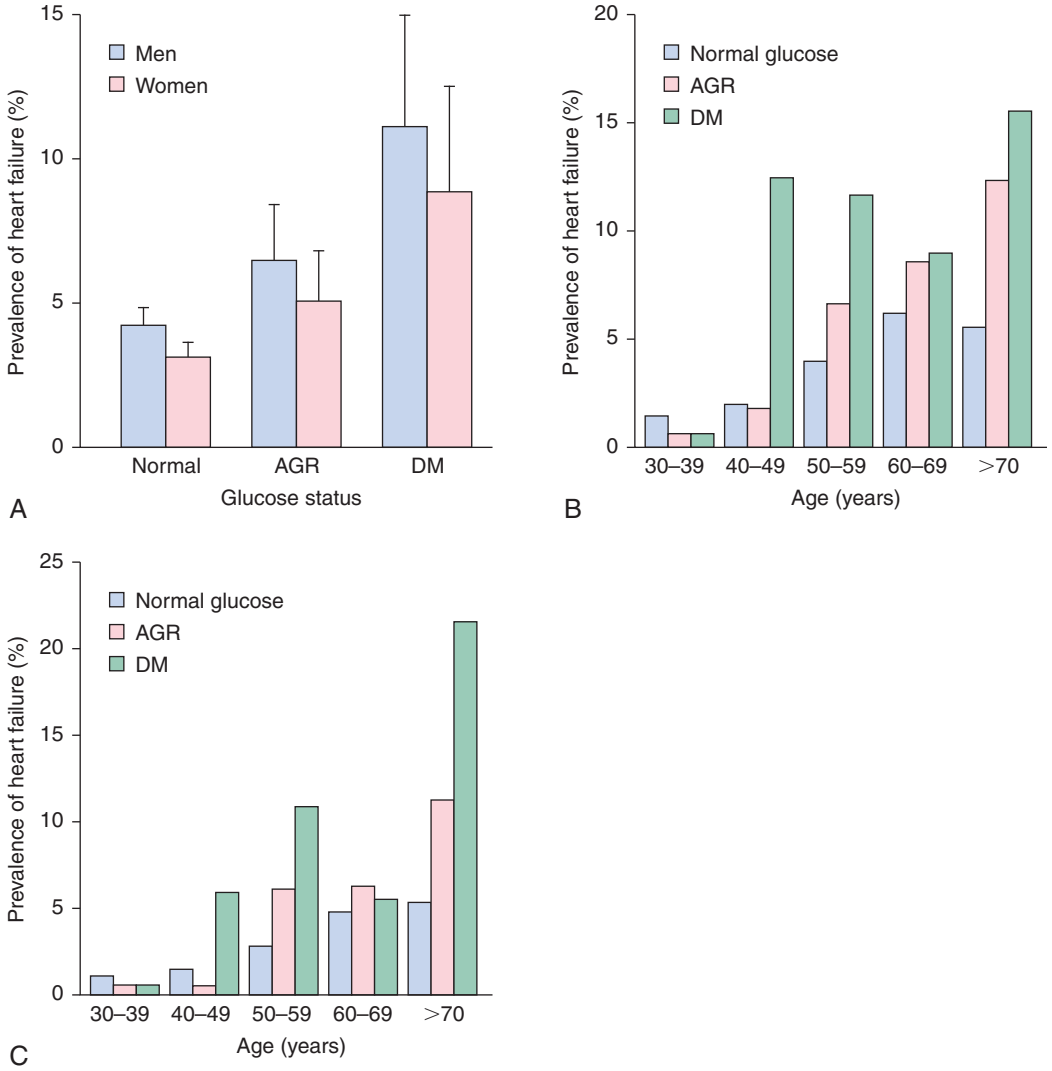


FIGURE 23-3 **A,** Age-adjusted prevalence of HF according to baseline glucose status (AGR = Abnormal glucose regulation: impaired glucose tolerance or impaired fasting glucose) in men and women. **B,** Prevalence of HF by age and glucose abnormalities in men. **C,** Prevalence of HF by age and glucose abnormalities in women. *(Modified from Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study,* Diabetes Care *28:612-616, 2005.)*

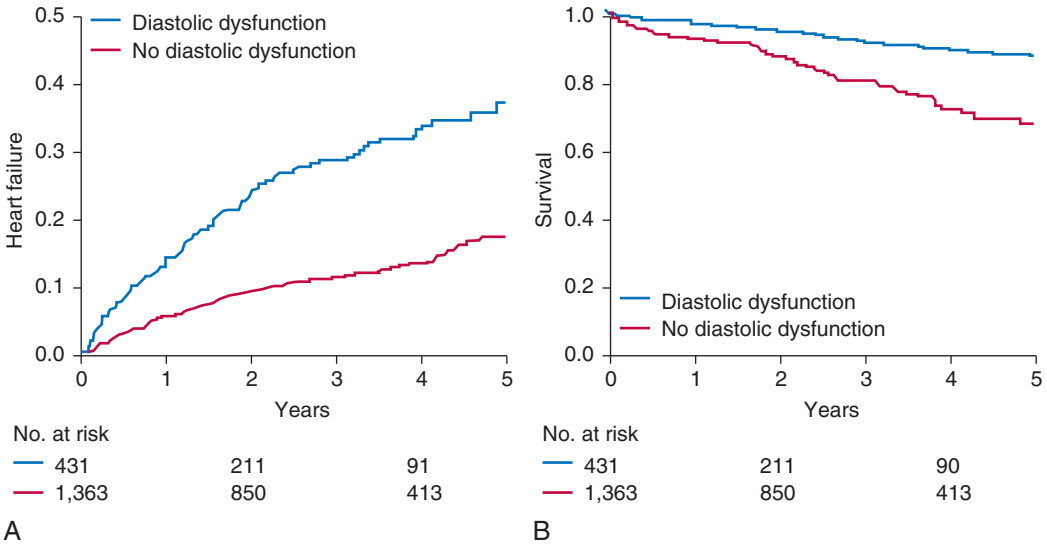


FIGURE 23-4 Kaplan-Meier analysis of diastolic dysfunction and subsequent heart failure (A) and mortality (B) in diabetic patients free of clinical HF at baseline. Diastolic dysfunction defined as passive transmitral LV inflow velocity to tissue Doppler imaging velocity of the medial mitral annulus during passive filling (E/e') ratio above 15. *(Modified from From AM, Scott CG, Chen HH: The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study,* J Am Coll Cardiol *55:300-305, 2010.)*

diabetes in HF patients increased markedly over a 20-year period (3.8% per year).[44] Other studies have suggested that the prevalence of diabetes may be even greater in hospitalized patients. In a large registry of patients with acute decompensated HF, 44% of patients had a history of diabetes.[45] Similarly, in individuals hospitalized with HF and normal ejection fraction (EF), 33% to 46% of individuals had diabetes.[46,47] The prevalence of DM in HF clinical trials ranges from 20% to 36%, depending on the patient population studied.[48–53] It is important to recognize that some individuals with diabetes may be excluded from clinical trials because of exclusion of certain comorbid conditions (such as significant renal dysfunction).

The prevalence of diabetes in HF populations may be even greater when systematic diabetes screening occurs and individuals with previously unrecognized diabetes are identified. In a cohort of outpatients with systolic HF who underwent systematic oral glucose tolerance testing, almost 20% of individuals without a prior diagnosis of diabetes were found to have newly diagnosed diabetes.[54]

INCIDENT DIABETES IN PATIENTS WITH HEART FAILURE

Increasing evidence also suggests that HF itself may be considered an insulin-resistant state and that patients with established HF are at increased risk for the development of diabetes. In nondiabetic HF patients enrolled in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program[55] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF),[56] the incidence of diabetes was approximately 28 cases and 21 cases per 1000 patient-years of follow-up, respectively, an incidence that is higher than the incidence rates described in unselected U.S. adults aged 45 to 79 years (estimated incidence rates 12.4 to 13.5/1000 patient-years).[57] The potential reasons for this association between HF and greater rates of incident diabetes have not been well established. Clinical predictors of incident diabetes in HF patients include elevated body mass index and waist circumference, increased serum alanine aminotransferase (ALT), elevated glucose or HbA1c, diuretic therapy, digoxin therapy, lower serum creatinine concentration, and more severe New York Heart Association (NYHA) class.[55,58,59] Other potential explanations for the greater rates of diabetes in patients with established HF include increased neurohormonal activation promoting both skeletal and myocardial insulin resistance.[60] Experimental data have also demonstrated that sympathetic activation in HF may contribute to insulin resistance through upregulation of p53 expression in adipose tissue and associated adipose inflammation and lipolysis.[61]

DIABETES AND ADVERSE OUTCOMES IN HEART FAILURE PATIENTS

Heart Failure Hospitalization

Multiple studies have demonstrated that the presence of diabetes in patients with established HF is associated with greater rates of future HF hospitalization than in HF patients without diabetes (**Fig. 23-5**).[62] For example, in the Candesartan Heart Failure Assessment of Reduction (CHARM) program, rates of HF hospitalization in patients with diabetes were approximately twice the rates in those without diabetes (139.3 versus 68.2 HF hospitalizations/1000 patient-years).[50] Other HF studies have also demonstrated significantly increased rates of HF hospitalization in patients with diabetes compared with those without diabetes.[49,51,53,63] In survivors of acute myocardial infarction (MI) complicated by LV dysfunction or symptoms of HF, diabetes is also associated with approximately twofold greater rates of subsequent HF hospitalization.[48,52,64] The increased rates of HF hospitalization after MI occur despite similar infarct size and LVEF at baseline in patients with and without diabetes and no greater enlargement or reduction in systolic volume over time in patients with diabetes compared with those without diabetes.[65,66]

In patients hospitalized with acute decompensated HF, diabetes is independently associated with a longer hospital stay.[67]

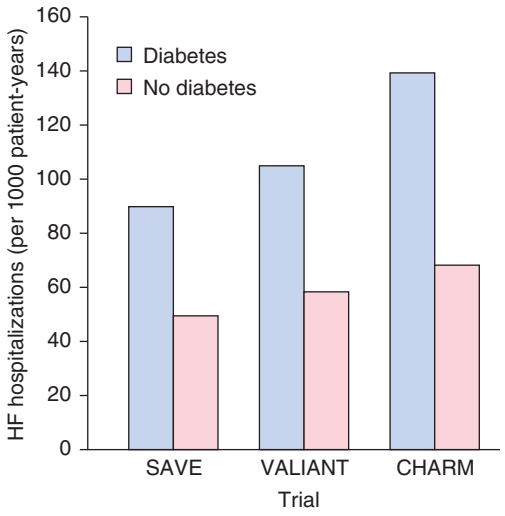


FIGURE 23-5 Hospitalizations in HF patients with and without diabetes. Rate of heart failure hospitalizations per 1000 patient-years. CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; SAVE = Survival and Ventricular Enlargement; VALIANT = Valsartan in Acute Myocardial Infarction. *(Modified from Nasir S, Aguilar D: Congestive heart failure and diabetes mellitus: balancing glycemic control with heart failure improvement,* Am J Cardiol *110:50B-57B, 2012.)*

Mortality

The development of HF in a person with diabetes is associated with a markedly increased risk of death compared with diabetic individuals who remain free of HF. In a study of older individuals (65 years), incident HF was associated with markedly reduced survival compared with those diabetic individuals who remained HF free (mortality rate 32.7/100 person-years compared with 3.7/100 person-years, respectively; HR of death 10.6, 95% CI 10.4-10.9) (**Fig. 23-6**).[14] In a more recent analysis of almost 8000 individuals with diabetes, prevalent HF was associated with a 69% greater risk of death compared with diabetic individuals without HF.[68]

In both epidemiologic studies[44,69–71] and analyses of clinical trials of patients with established HF,[42,48,50,52,72–75] individuals with diabetes have increased mortality compared with individuals without diabetes (**Table 23-3**; **Fig. 23-7**).

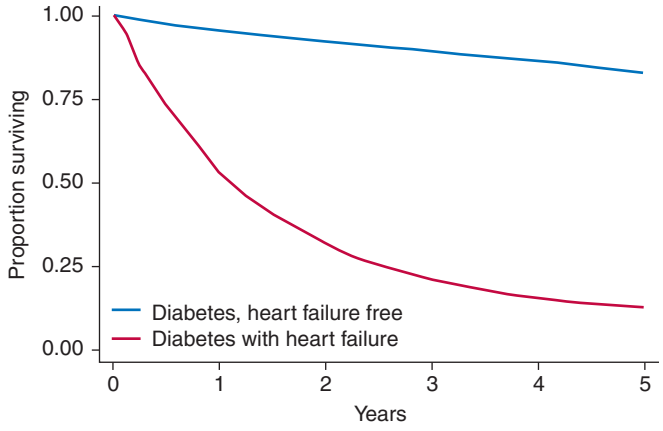


FIGURE 23-6 Five-year Kaplan-Meier survival estimates for 115,803 adults aged 65 years or older in fee-for-service Medicare with diabetes by incident heart failure status. *(Modified from Bertoni AG, Hundley WG, Massing MW, et al: Heart failure prevalence, incidence, and mortality in the elderly with diabetes,* Diabetes Care *27:699-670, 2004.)*

Both CV mortality and non-CV mortality are increased in HF patients with diabetes compared with HF patients without diabetes.[43,50,69] In a contemporary meta-analysis of 31 studies with more than 41,000 HF patients, diabetes was independently associated with total mortality (HR 1.41, 95% CI 1.35-1.47) and CV death (1.51, 95% CI 1.41-1.62).[43] In addition, the incidence of each mode of CV death (i.e., death from MI, sudden death, HF, and stroke) is elevated in those with diabetes compared with those without diabetes.[50] Insulin use has been associated with increased mortality in diabetic patients with established HF,[52,72,76] although, as described earlier, this may be a reflection of diabetes disease severity rather than a direct mediator.

In individuals with diabetes and established HF, the relationship between glycemic control and mortality remains poorly understood. Several studies have demonstrated a paradoxical relationship (U-shaped or inverse relationship) between levels of HbA1c and mortality in patients with diabetes and HF.[77–79] In a study of 5815 ambulatory HF patients receiving medical treatment for diabetes, individuals with modest glycemic control (HbA1c above 7.1% to 7.8%) had lower mortality compared with individuals whose HbA1c levels were either higher or lower (**Fig. 23-8**).[77] In smaller cohorts of diabetic individuals with advanced systolic HF, higher HbA1c levels have been paradoxically associated with improved survival.[78,79] The explanation for these results in observational studies is not fully understood, but it is possible that lower HbA1c levels in HF patients with diabetes may be a marker of more severe disease or cardiac cachexia or may reflect differences in baseline characteristics. In addition, not all studies have demonstrated a paradoxical relationship between HbA1c and increased mortality in HF patients; in 2412 participants (of whom 907 participants had known diabetes) enrolled in the CHARM study, increasing levels of HbA1c were associated with increased risk of total mortality, HF hospitalization, and a composite outcome of CV death or HF hospitalization.[80] Of note, the graded relationship between HbA1c and mortality was more pronounced in the nondiabetic patients enrolled in CHARM and did not reach statistical significance for the outcomes of CV death (P for heterogeneity = 0.04) and total mortality in the cohort of HF patient with diabetes (P for heterogeneity = 0.008).[80]

Special Population: Women

Some studies have found that the presence of DM may have greater impact on cardiac structure and function in women than in men.[40,81] In the Framingham Heart Study, LV mass and left atrial size increased across categories of worsening glucose tolerance and was more striking in women than in men.[40] Other studies have failed to demonstrate an interaction between diabetes and cardiac structure and function in women compared with men.[37,82,83]

Studies have also suggested that diabetes may be associated with greater risk of incident HF in women than in men. In the Framingham Heart Study, diabetes was associated with a fourfold increased risk of HF in women compared with an almost twofold increased risk in men.[1] The population attributable risk for DM was reported as 6% for men and 12% for women in the Framingham Heart Study.[2] In contrast, other epidemiologic studies have not demonstrated that the diabetes attributable risk for incident HF is greater in women than in men.[4,8]

TABLE 23-3 Mortality in Patients with Diabetes and Established Heart Failure (HF) in Selected Population-Based Studies and Clinical Trials

STUDY	YEAR OF PUBLICATION	SAMPLE SIZE	MULTIVARIATE ADJUSTED RISK FOR DEATH (COMPARED WITH INDIVIDUALS WITHOUT DM)	COMMENT
Population-Based Studies				
Framingham[71]	1993	9405	Women: HR 1.70 (95% CI 1.21-2.38) Men: HR 0.99 (95% CI 0.70-1.40)	
Rotterdam[70]	2001	5540	Age-adjusted HR 3.19 (95% CI 1.80-2.26)	
Olmsted County[44]	2006	665	RR 1.33 (95% CI 1.07-1.66)	DM and no CAD: RR 1.79 (95% CI 1.33 to 2.41) DM and CAD: RR 1.11 (95% CI 0.81 to 1.15)
United Kingdom[69]	2013	1091	HR 1.72 (95% CI 1.29-2.28)	Association between DM and increased mortality is similar in those with ischemic and nonischemic CMP.
Clinical Trials				
SOLVD[73]	1991	6797 (reduced LVEF)	RR: 1.37 (95% CI 1.21-1.55) in those with ischemic CMP RR 0.98 (95% CI 0.76-1.32) in those without ischemic CMP	
DIAMOND[74]	2004	5491	RR 1.5 (95% CI 1.3-1.8) total cohort RR 1.4 (95% CI 1.3-1.6) men RR 1.7 (95% CI 1.4-1.9) women	Excess mortality associated with DM was greater in women than in men.
VALIANT[48]	2004	14,703 (acute MI and HF)	HR 1.43 (95% CI 1.29-1.59) with previously diagnosed DM HR 1.50 (95% CI 1.21-1.85) with newly diagnosed DM	Individuals with newly diagnosed DM had similar mortality at 1-year compared with individuals with previously diagnosed DM.
CHARM[50,72]	2006	7500	HR (DM, no insulin): 1.60 (95% CI 1.34-1.68) HR (DM, on insulin): 1.80 (95% CI 1.56-2.08) HR (DM, preserved EF): 1.84 (95% CI 1.51-2.26) HR (DM, reduced EF): 1.55 (95% CI 1.38-1.74)	The association between DM and increased mortality was similar between HF patients with reduced LVEF and those with preserved LVEF. The association between DM and mortality was not modified by gender or cause of HF.
I-PRESERVE[75]	2011	4128 (HF with preserved EF)	HR 1.43 (1.2, 1.60)	

CMP = Cardiomyopathy; DIAMOND = Danish Investigations of Arrhythmia and Mortality on Dofetilide; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction; SOLVD = Studies of Left Ventricular Dysfunction.

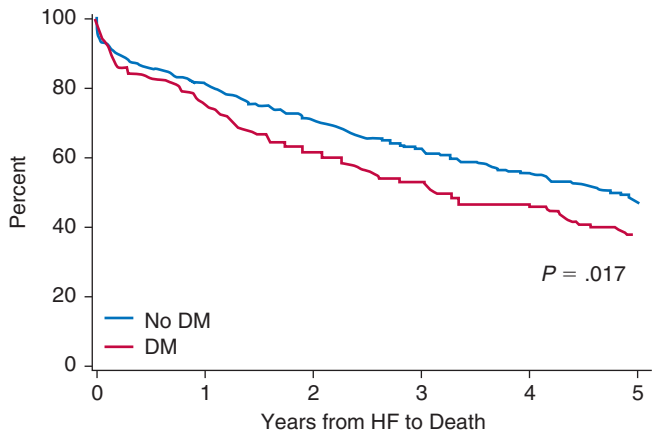


FIGURE 23-7 Kaplan-Meier survival estimates in HF patients with and without DM. *(Modified from From AM, Leibson CL, Bursi F, et al: Diabetes in heart failure: prevalence and impact on outcome in the population,* Am J Med *119:591-599, 2006.)*

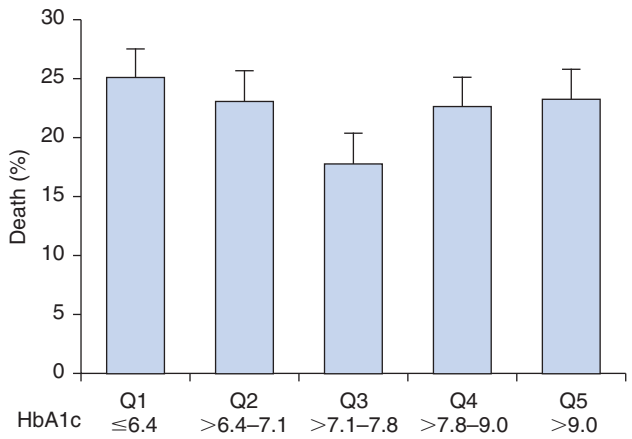


FIGURE 23-8 The graph represents the proportion of HF patients who died during 2-year follow-up by quintiles (Q) of glycosylated hemoglobin (HbA1c). Global chi-square, $P = 0.001$. Error bars indicate 95% CI. *(Modified from Aguilar D, Bozkurt B, Ramasubbu K, Deswal A: Relationship of hemoglobin A1c and mortality in heart failure patients with diabetes,* J Am Coll Cardiol *54:422-428, 2009.)*

In populations with established HF, the excess risk in diabetic patients may be particularly prominent in women,[74] although this finding has not been consistently observed.[50] In a meta-analysis of more than 40,000 patients with HF, DM was a strong, independent predictor of mortality in both men and women, but the presence of diabetes attenuated the protective effect of female sex on overall prognosis in women with established HF.[43]

Etiology of Heart Failure

Although some studies have suggested that diabetes may have greater prognostic significance in individuals with HF because of the presence of ischemic heart disease,[49,73] these findings have not been confirmed in other studies.[44,50,69]

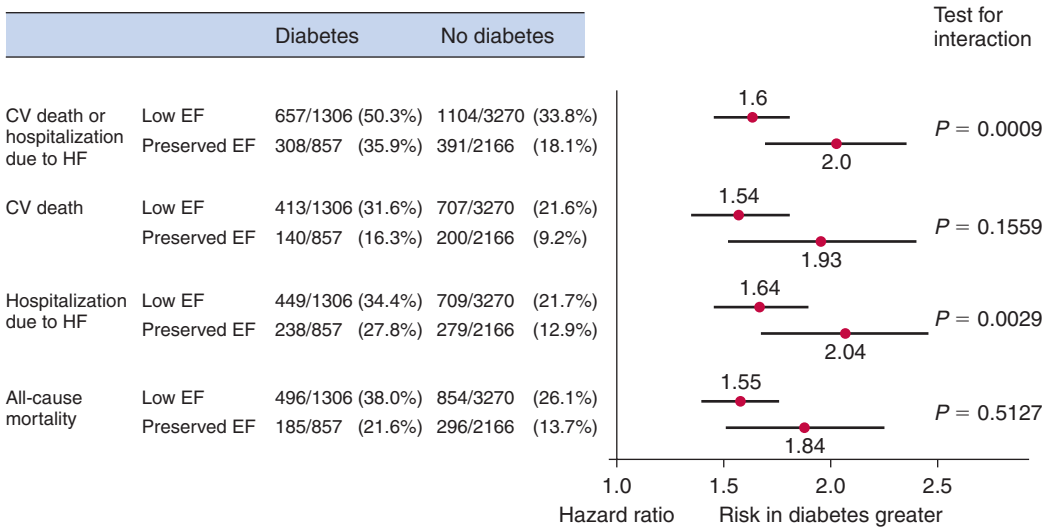


FIGURE 23-9 Adjusted HR of different outcomes associated with diabetes. Horizontal bars represent 95% CI. *(Modified from MacDonald MR, Petrie MC, Varyani F, et al: Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme,* Eur Heart J *29:1377-1385, 2008.)*

Heart Failure with Preserved Left Ventricular Ejection Fraction

As previously described, abnormalities of increased LV mass, increased left atrial size, and diastolic Doppler abnormalities are commonly present in individuals with diabetes, and these diastolic abnormalities are associated with greater rates of HF (see **Fig. 23-4**).[41] In the Framingham Heart Study, diabetes was a risk factor for both systolic HF and HF with preserved EF.[84] In patients with HF with preserved EF, the presence of diabetes is associated with increased mortality,[47,50,75] and the increased mortality risk associated with diabetes is similar in HF patients with preserved LVEF compared with patients with reduced LVEF.[47,50] Diabetes does appear to confer a greater risk for HF hospitalization in HF patients with preserved LVEF compared with those with low EF. In the CHARM program, the adjusted HR for HF hospitalization in diabetic versus nondiabetic patients was 1.64 (95% CI 1.44-1.86) in patients with low EF and 2.014 (95% CI 1.68-2.07) in patients with preserved EF (**Fig. 23-9**).[50]

SUMMARY

Multiple studies have demonstrated that DM is associated with increased risk for the development of HF in a variety of populations. The prevalence of HF in individuals with type 2 diabetes is greater than estimates in the general population, and prevalence rates increase with age and other comorbid conditions. In patients with established HF, diabetes may be present in 12% to 40%, and its occurrence may be even higher in populations such as those with acute decompensated HF. The prevalence of diabetes in HF patients may be even higher when systematic screening for diabetes is performed. It is important to note that the coexistence of diabetes and HF is associated with increased mortality and morbidity compared with HF patients without diabetes or compared with diabetic patients without HF. This increased hazard is seen throughout the spectrum of HF, including HF with preserved EF and HF with reduced EF.

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24 Diabetic Cardiomyopathy

Mediators and Mechanisms

Pavan K. Battiprolu, Zhao V. Wang, and Joseph A. Hill

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SCOPE OF THE PROBLEM

Heart disease is the greatest noninfectious health hazard ever to confront the human race. Rampant for some years in the developed world, this epidemic is spreading rapidly around the globe. As one prominent example, it is estimated that 5 million Americans have heart failure (HF), a syndrome with a 5-year mortality of approximately 50%.[1] Indeed, HF has remained the leading cause of death in industrialized nations for several years. Accordingly, HF, the end result of disease-related remodeling of the myocardium, is responsible for a huge societal burden of morbidity, mortality, and cost.

Numerous events contribute to the rise in HF, but the increasing prevalence of diabetes is a significant contributor. For one, cardiovascular disease, including HF, is the leading cause of morbidity and mortality in patients with diabetes (see also **Chapter 23**). Although the underlying causes of diabetes-associated heart disease are multifactorial, the importance of ventricular dysfunction independent of coronary artery disease (CAD) or hypertension, a condition termed *diabetic cardiomyopathy*, has been emphasized.[2–4] The diabetes and cardiovascular communities embraced the concept of diabetic cardiomyopathy as a distinct entity in the early 1970s when autopsy specimens from diabetic patients with nephropathy revealed a myopathic process in the absence of epicardial CAD.[5] Over the years, substantial evidence has accumulated that a specific, discrete diabetic cardiomyopathy, distinct from ischemic injury, does indeed exist. The exact prevalence, nature, and cause of cardiac dysfunction directly attributable to diabetes per se have given rise to considerable debate, inasmuch as the disease is associated with numerous comorbidities, including hypertension, coronary atherosclerosis, and microvascular dysfunction.

Constant and unremitting metabolic stress on the heart leads over time to progressive deterioration of myocardial structure and function. This suggests that therapeutic interventions early in the disease, targeting specific metabolic and structural derangements, may be required. This is especially relevant because rigid control of hyperglycemia, however central to treatment, has not fulfilled hopes of meaningful morbidity and mortality benefit.[6] Recent and ongoing research into mechanisms of metabolic control, insulin resistance, and diabetes-associated derangements portend novel therapies designed to benefit the rapidly expanding cohort of patients with diabetes, a benefit with tremendous societal impact. Current therapies are insufficient to arrest the progression of HF. Developing new therapies will require greater understanding of molecular events underlying pathologic cardiac remodeling. Substantial work will be required to elucidate the role(s) of specific molecular mechanisms in the pathogenesis of diabetes-induced remodeling. It is our hope that insights gleaned from such studies will lead to identification of therapeutic targets with clinical relevance.

EPIDEMIOLOGICAL EVIDENCE

The incidence and prevalence of diabetes mellitus (DM) are both rising rapidly (see also **Chapter 1**).[7] DM affects 350 million people around the world, and the World Health Organization (WHO) has projected that diabetes-related deaths will double between 2005 and 2030 (www.who.int/diabetes/en/). Within this burgeoning health care problem of worldwide proportions, obesity-related type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diagnosed diabetes in adults.[8] Furthermore, more than 60% of patients who present with symptomatic chronic heart disease have abnormal glucose homeostasis (see also **Chapter 23**).[9–11] Patients with DM and established cardiovascular disease have an unfavorable prognosis. In fact, diabetes and insulin resistance are powerful predictors of cardiovascular morbidity and mortality, and each is an independent risk factor for death in patients with established HF.[12]

The term *diabetic cardiomyopathy*, although admittedly vague, refers to the multifactorial manifestations of diabetes-related left ventricular (LV) failure characterized by both systolic and diastolic function (**Box 24-1**).[13] The Framingham Heart Study showed that men with diabetes

BOX 24-1 Diabetic Cardiomyopathy: Hallmark Features

Structural and Morphologic
Near-normal end-diastolic volume
Elevated left ventricular mass relative to chamber volume
Elevated wall thickness to chamber radius
Myocardial hypertrophy
Myocardial fibrosis
Intramyocyte lipid accumulation

Functional
Abnormal left ventricular diastolic function (observed in 75% of asymptomatic diabetic patients)[146]
Compromised left ventricular systolic function
Reduced ventricular elasticity
Clinical heart failure

Data from Boudina S, Abel ED: Diabetic cardiomyopathy revisited, *Circulation* 115:3213-3223, 2007.

are twice as likely to develop HF as their nondiabetic counterparts, and women with diabetes have a fivefold increase in the rate of HF. The clinical spectrum of HF ranges from asymptomatic to overt symptoms at rest. Diabetes complicated by hypertension represents a particularly high-risk group for the development of HF.[14] Diastolic dysfunction is common (>50% prevalence in some studies) and can sometimes be linked to diabetes in the absence of concomitant hypertension.

Echocardiographic studies confirm that diastolic abnormalities occur in young diabetic patients who have no known diabetic complications.[15] One study reported that patients with diabetes manifest early findings of systolic dysfunction preceding echocardiographically detectable changes in LV ejection fraction.[15] Patients with diabetes who are also hypertensive have increased LV mass when compared with their nondiabetic counterparts, and LV function may in fact be hyperdynamic.[15]

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

A number of molecular mechanisms have been proposed to contribute to the pathogenesis of diabetic cardiomyopathy.[16–20] However, evidence for a direct, causal link between insulin resistance, a hallmark of type 2 diabetes, and ventricular dysfunction has not been established. The natural history of diabetic cardiomyopathy has been broadly divided into two phases (**Table 24-1**).[19] Although the first phase represents short-term, physiologic adaptation to the metabolic alterations of diabetes, the second phase involves degenerative changes that the myocardium is unable to repair and that ultimately culminate in irreversible pathologic remodeling.

The hormone insulin is central to the control of intermediary metabolism, orchestrating substrate usage for storage or oxidation in all cells.[21] As a result, insulin has profound effects on both carbohydrate and lipid metabolism throughout the body, as well as significant influences on protein metabolism. Consequently, derangements in insulin signaling have widespread and devastating effects in numerous tissues, including the cardiovascular system. Insulin is the main hormone for regulation of blood glucose, and, in general, normoglycemia is maintained by precisely tuned insulin secretion. It is important to note that the normal pancreatic beta cell can adapt to changes in requirements for circulating insulin; when the downstream actions of insulin are hampered (e.g., in insulin resistance), the pancreas compensates by upregulating beta cell function (hyperinsulinemia). Relative insulin resistance occurs when the biologic actions of insulin are inadequate for both glucose disposal in peripheral tissues and suppression of hepatic glucose production.[22]

T2DM is typified by hyperglycemia, hyperinsulinemia, and obesity, and insulin resistance is a cardinal feature.[2] The disease itself arises from a variety of causes,[24] including dysregulated glucose sensing or insulin secretion (maturity-onset diabetes of the young), autoimmune-mediated beta cell destruction (type 1 diabetes mellitus [T1DM]), or insufficient compensatory insulin secretion in the setting of peripheral insulin resistance or T2DM, which accounts for 90% of diabetes. These events, acting through a variety of mediators such as altered intracellular calcium, increased reactive oxygen species (ROS), ceramides, hexosamines, and advanced glycation end products (AGEs), contribute to the pathogenesis of the disorder.[3] In addition, the interplay between dysregulated function of endothelial cells and fibroblasts contributes, highlighting the multifactorial etiology of diabetic cardiomyopathy. Recent studies have highlighted that transcriptional and metabolic derangements within the

TABLE 24-1 Natural History of Diabetic Cardiomyopathy

PHASE		MOLECULAR AND CELLULAR EVENTS	ALTERATIONS IN STRUCTURE AND MORPHOLOGY	MYOCARDIAL PERFORMANCE
I	Early	Metabolic disturbances: hyperglycemia, increased circulating free fatty acids, insulin resistance Altered Ca^{2+} homeostasis Endothelial dysfunction	Normal left ventricular dimensions, wall thickness, and mass	Impaired diastolic compliance with normal systolic function, or no obvious functional changes
	Middle	Cardiomyocyte injury, apoptosis, necrosis Activation of cardiac fibroblasts leading to myocardial fibrosis	Minor changes in structure: slightly increased heart mass, wall thickness, and/or ventricular dimensions Cardiomyocyte hypertrophy Insignificant myocardial vascular changes	Significant changes in diastolic and systolic function
II	Late	Hypertension Coronary artery disease Microangiopathy Cardiac autonomic neuropathy	Significant changes in structure: increased heart size, wall thickness, and mass Myocardial microvascular disease	Abnormal diastolic and systolic function

Data from Fang ZY, Prins JB, Marwick TH: Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications, *Endocr Rev* 25:543-567, 2004.

cardiomyocyte itself are important elements in the pathogenesis of the disorder, as well.[25]

The concept of diabetic cardiomyopathy is based on the notion that the disease, DM, itself is a key factor eliciting changes at the molecular and cellular levels of the myocyte, culminating in structural and functional abnormalities in the heart. In other words, the diabetic milieu is toxic to the myocyte, above and beyond contributions from ischemia (CAD) or pressure stress (hypertension). Whereas the cause of diabetic cardiomyopathy is multifactorial and incompletely characterized, progress has been made in recent years to define underlying mechanisms (**Fig. 24-1**).[5] As a result, several novel molecular targets with potential therapeutic relevance have been proposed (**Fig. 24-2**).

Cardiomyocytes are capable of metabolizing a spectrum of substrates. The myocardium as a "metabolic omnivore" normally relies on metabolism of fatty acids (FAs) and glucose, and to a lesser extent lactate and ketone bodies, to produce adenosine triphosphate (ATP).[26] These substrates, however, are unable to enter the cardiomyocyte by simple diffusion and must be taken up by facilitated transport. FA uptake is mediated by FAT (fatty acid translocase; also known as cluster of differentiation 36 [CD36]), and glucose intake is accomplished by both GLUT-1 and GLUT-4 (glucose transporter types 1 and 4). In response to availability of nutrients or increased cardiac work, plasma insulin concentrations rise.[27] This, in turn, provokes translocation of both GLUT-4 and FAT to the myocyte sarcolemma. To date, several studies have implicated signaling pathways that regulate GLUT-4 translocation with those involved in transport of FAT to the sarcolemma.[27,28] However, during the development of insulin resistance and T2DM, FAT becomes preferentially sarcolemma-localized, whereas GLUT-4 remains internalized. This reciprocal positioning of GLUT-4 and FAT is central to aberrant substrate uptake in the diabetic heart, where FA metabolism is chronically increased at the expense of glucose.[27,28] Moreover, dyslipidemia triggered by insulin resistance provokes increases in systemic free FAs, which in turn promote uptake and usage of fat in cardiomyocytes. In addition, the interplay of preferential substrate usage is affected by a variety of other mediators, as previously reviewed.[3]

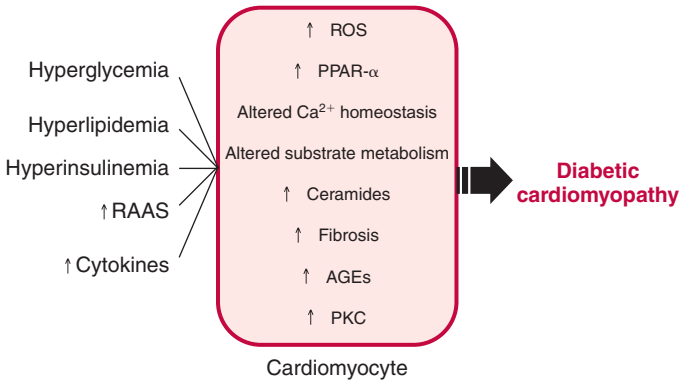


FIGURE 24-1 The cause of diabetic cardiomyopathy is multifactorial. An overview of triggers, mediators, and consequences involved in the pathogenesis of diabetic cardiomyopathy. AGEs = Advanced glycation end products; PKC = protein kinase C; PPAR-α = peroxisome proliferator-activated receptor alpha; RAAS = renin-angiotensin-aldosterone system. *(Modified from Rubler S, Dlugash J, Yuceoglu YZ, et al: New type of cardiomyopathy associated with diabetic glomerulosclerosis,* Am J Cardiol *1972;30:595-602, 1972.)*

Hyperglycemia and Glucotoxicity

Hyperglycemia, a consequence of combined decreased glucose clearance plus augmented hepatic gluconeogenesis, plays a central role in the pathogenesis of diabetic cardiomyopathy. In patients with T2DM, endogenous glucose production is accelerated.[29] Because this increase occurs in the presence of hyperinsulinemia, at least in the early and intermediate stages of disease, hepatic insulin resistance is a driving force of hyperglycemia.

Chronic hyperglycemia promotes glucotoxicity, which contributes to cardiac injury through multiple mechanisms, including direct and indirect effects of glucose on cardiomyocytes, cardiac fibroblasts, and endothelial cells. Chronic hyperglycemia promotes the overproduction of ROS through the electron transport chain, which can induce apoptosis[30] and activate poly (adenosine diphosphate-ribose) polymerase 1 (PARP). This enzyme mediates the direct ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH), diverting glucose from the glycolytic pathway toward alternative biochemical cascades that participate in hyperglycemia-induced cellular injury. These include increases in AGEs and the activation of the hexosamine

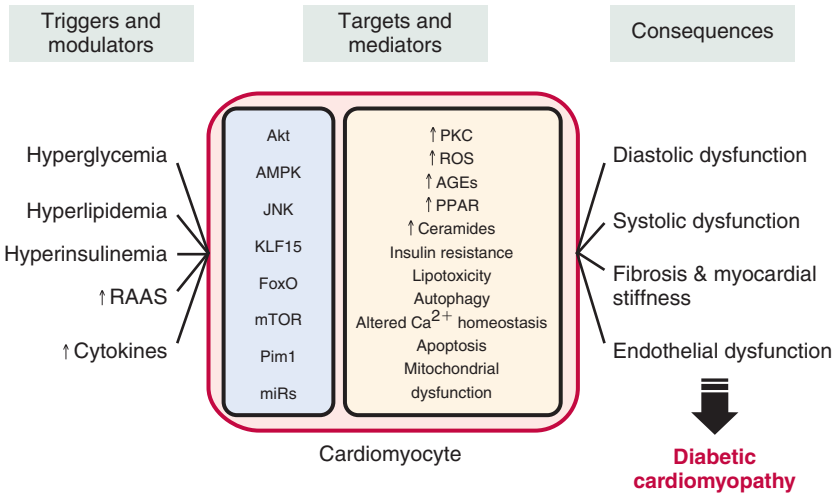


FIGURE 24-2 New molecular targets and their role in diabetic cardiomyopathy. An overview of triggers, mediators and consequences involved in the pathogenesis of diabetic cardiomyopathy. AGEs = Advanced glycation end products; FoxO = forkhead box O protein; KLF = Krüppel-like factor; mTOR = mammalian target of rapamycin; PKC = protein kinase C; PPAR = peroxisome proliferator-activated receptor; RAAS = renin-angiotensin-aldosterone system.

biosynthetic pathway, the polyol pathway, and protein kinase C.[30,31] Hyperglycemia-induced apoptosis is stimulated by ROS,[32] PARP,[33] AGEs,[34] and aldose reductase.[35] Hyperglycemia also contributes to altered cardiac structure and function through post-translational modification of extracellular matrix components (e.g., collagens) and altered expression and function of both the ryanodine receptor (RyR) and sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA), which in aggregate contribute to decreased systolic and diastolic function.[30]

Hyperlipidemia and Lipotoxicity

Enhanced lipid synthesis in hepatocytes and increased lipolysis in adipocytes together lead to increases in circulating FAs and triglycerides (TGs) in patients with diabetes. Also, insulin stimulates FA transport into cardiomyocytes.[36] Thus the combination of elevated circulating lipids plus hyperinsulinemia increases FA delivery to cardiac cells, which rapidly adapt by promoting FA use. However, if FA delivery overtakes the oxidative capacity of the cell, FAs accumulate intracellularly, promoting lipotoxicity.[37]

Several major mechanisms contribute to cardiac lipotoxicity.

- *ROS generation.* High rates of FA oxidation increase mitochondrial membrane potential, leading to the production of ROS, which under normal physiologic conditions are removed by molecular antioxidants and antioxidant enzymes. However, cardiomyocyte damage and death by apoptosis ensue if the generation of ROS exceeds their degradation, leading to ROS accumulation (oxidative stress).[38]
- *Ceramide production.* Accumulation of intracellular lipids can contribute directly to cell death under conditions in which FAs are not metabolized.[39] Reaction of palmitoyl CoenzymeA (CoA) with serine leads to the generation of ceramide, a sphingolipid that can trigger apoptosis through inhibition of the mitochondrial respiratory chain.[40]
- *Insulin resistance.* Diacylglycerol, ceramide, and fatty acyl-CoA can each activate a negative regulatory signaling pathway involving the atypical protein kinase C-θ and IκB kinase (IKK). Both kinases, in turn, stimulate serine phosphorylation of the insulin receptor substrate (IRS), impairing insulin signaling.[41]
- *Impaired contractility.* Intracellular FA accumulation can trigger opening of the K-ATP channel, leading to action potential shortening. This in turn diminishes the duty cycle of the L-type Ca^{2+} channel, leading to reduced sarcoplasmic reticular Ca^{2+} stores and depressed contractility.[42]

Thus, high FA uptake and metabolism not only stimulate accumulation of FA intermediates but also increase oxygen demand, provoke mitochondrial uncoupling and ROS generation, decrease ATP synthesis, induce mitochondrial dysfunction, and trigger apoptosis. Together, these events participate importantly in the pathogenesis of diabetic cardiomyopathy.

Hyperinsulinemia, Insulin Resistance, and Altered Substrate Metabolism

Early clinical studies reported an association between systemic hyperinsulinemia and development of cardiac hypertrophy.[43,44] Potential mechanisms include crosstalk between insulin-dependent signaling and pro-growth pathways in the heart. For example, the signaling cascade activated by insulin shares common elements with the neurohormonal growth agonists insulin-like growth factor 1 (IGF-1) and angiotensin II (Ang II).[45] These pathways, in turn, activate both the ERK and phosphoinositide 3-kinase, Protein Kinase B, mammalian target of rapamycin (PI3K/PKB/Akt/mTOR) cascades, each of which is involved in regulating cell growth and protein synthesis. Activation of the PI3K/PKB/Akt/mTOR) pathway is associated with development of physiologic hypertrophy, whereas ERK signaling, along with the Protein Kinase C, PKC; Nuclear factor of activated T-cells, NFAT (PKC and calcineurin/NFAT) pathways, triggers pathologic hypertrophy.[45] Also, activation of the sympathetic nervous system (SNS) and the renin-angiotensin aldosterone system (RAAS) have each been reported in diabetes, leading to enhanced stimulation of both adrenergic and angiotensin receptor 1 (AT1).[19,46] Chronic hyperinsulinemia may augment myocardial Akt-1 indirectly through increased SNS activation[47] or by triggering the Ang II pathway.[48]

In the normal heart, approximately two thirds of the energy required for cardiac contractility derives from FA oxidation, with the remainder deriving from glucose and lactate metabolism. By contrast, in conditions of insulin resistance or diabetes, myocardial glucose use is significantly reduced, and a greater proportion of substrate usage shifts to beta-oxidation of FA.[49] Associated with the reduction in glucose use by diabetic myocardium is depletion of the glucose transporter proteins GLUT-1 and GLUT-4. Indeed, altered myocardial substrate metabolism favoring FAs over glucose as an energy source has been identified as a metabolic target of relevance. The diabetic heart relies on FA oxidation and is unable to switch to glucose, despite its lower oxygen consumption requirement. As a consequence, cardiac efficiency, the ratio of cardiac work to myocardial oxygen consumption, decreases; decreased cardiac efficiency has been reported in humans and experimental animals with diabetes (**Fig. 24-3**).[16–18,20]

Insulin resistance is defined as diminished insulin-dependent stimulation of muscle glucose uptake.[16–18,20] Underlying mechanisms include accumulation of FAs, which impairs insulin-mediated glucose uptake through inhibition of IRS and Akt. The serine protein kinases PKC-θ and IκB kinase (IKK), which elicit serine phosphorylation of IRS, are activated.[50] Phosphorylation and activation of PI3K and Akt are reduced, with significant consequences on the metabolic effects of insulin in the heart.[51]

Abnormalities in Intracellular Ca^{2+} Homeostasis

Precise control of intracellular Ca^{2+} homeostasis is central to the regulation of myocardial function and growth.[52] During each heartbeat, Ca^{2+} enters the cardiomyocyte through L-type channels. The resulting increase in intracellular Ca^{2+} triggers further Ca^{2+} release from the sarcoplasmic/endoplasmic reticulum (SR) through the RyR, raising Ca^{2+} levels around the sarcomere. Binding of Ca^{2+} to troponin C in the contractile apparatus, in turn, initiates actin-myosin cross-bridging and myocardial contraction. Ca^{2+} reuptake into the SR by sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) and consequent declines in cytoplasmic Ca^{2+} allow for muscle relaxation.[52] Oxidative stress, accumulation of long-chain acetylcarnitines, and abnormal membrane lipid content also contribute to abnormalities of Ca^{2+} handling in diabetic cardiomyopathy.[18] Alterations in the function or expression of

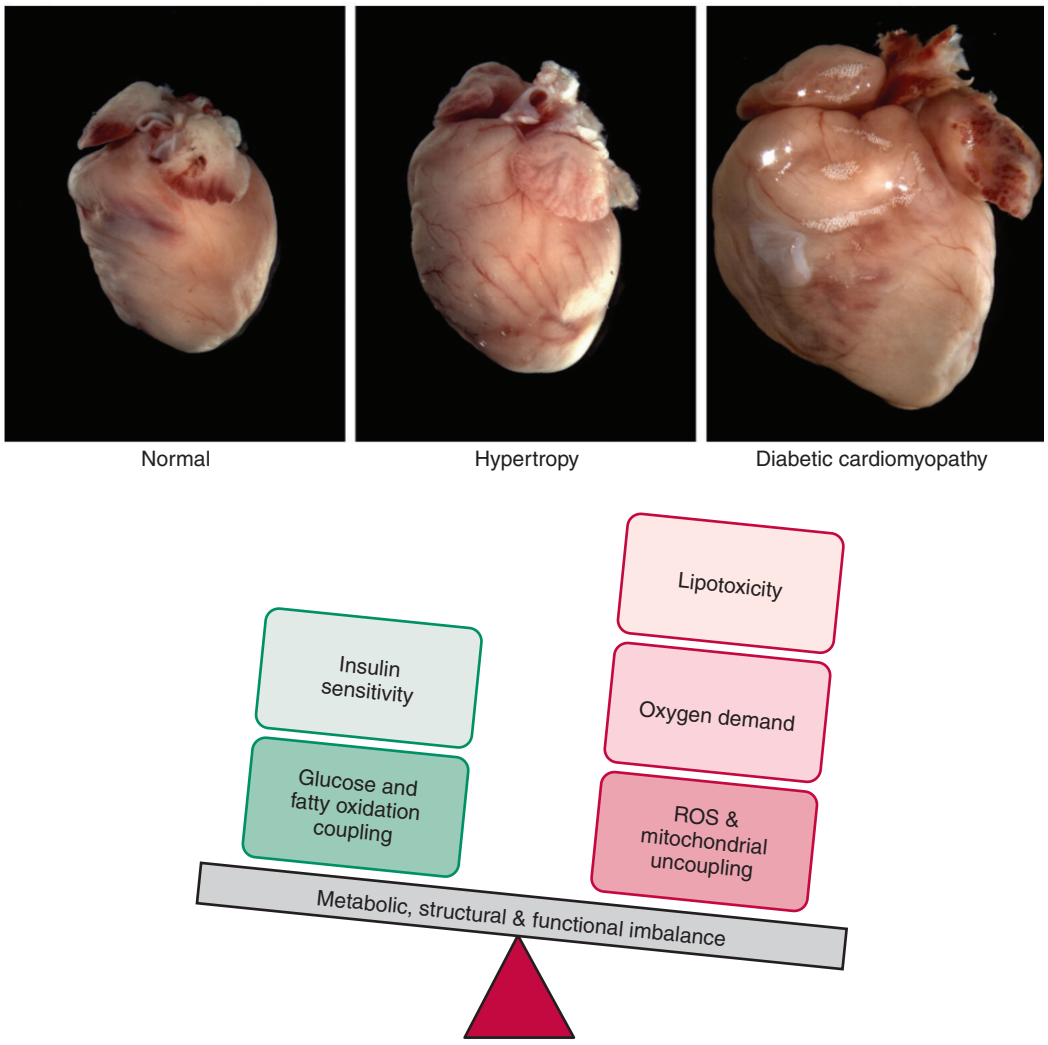


FIGURE 24-3 Metabolic events participating in diabetic cardiomyopathy. *Top,* Gross morphology of fixed mouse hearts collected over the course of exposure to high-fat diet. *Bottom,* Schematic depiction of key factors involved in metabolic, structural, and functional remodeling in diabetic cardiomyopathy.

SERCA, Na-K-ATPase (sodium-potassium adenosine triphosphatase), Na^+/Ca^{2+} exchanger, and RyR have each been observed in animal models of diabetes,[52–55] and cardiac overexpression of SERCA improves Ca^{2+} homeostasis and contraction in diabetic mice.[57]

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction contributes to progression of diabetes and diabetic cardiomyopathy.[58] However, mechanisms whereby mitochondrial dysfunction contributes to diabetic cardiomyopathy are poorly understood. For one, hyperglycemia-induced mitochondrial ROS generation has been implicated.[16–18,20] Mitochondrial oxidative metabolism is the major source of ATP production in the heart. Acetyl-CoA generated from either FA oxidation or glycolysis is metabolized in the tricarboxylic acid cycle to produce nicotinamide adenine dinucleotide-reduced (NADH) and flavin adenine dinucleotide-reduced (FADH2). These electron carriers transfer electrons to the mitochondrial electron transport chain, where ATP and ROS are generated. Increased ROS generation in the setting of high FA oxidation induces pathologic accumulation of ROS and consequent oxidative stress and cell damage.[16–18,20] Furthermore, it has been reported that p53 contributes to cardiac dysfunction in diabetes by promoting mitochondrial oxygen consumption, ROS production, and lipid accumulation.[59] The *SCO2* (synthesis of cytochrome c oxidase 2) gene is a transcriptional target of p53, and this protein plays a key role in the assembly of mitochondrial respiration complex IV. Nakamura and colleagues reported a marked increase in cardiac SCO2 expression in diabetic mice that contributed to increases in mitochondrial respiration rate.[59] This elevated mitochondrial activity triggers enhanced lipid uptake that exceeds mitochondrial oxidation capacity, leading to lipid accumulation and increased mitochondrial ROS production, together culminating in cardiac dysfunction. Reports from some studies also suggest that hyperglycemia promotes production of Rac1-mediated increases in nicotinamide adenine dinucleotide phosphate-reduced (NADPH) in addition to mitochondria-derived ROS,[60] each promoting accelerated apoptosis. The activation of NADPH oxidase by Rac1 can induce myocardial remodeling and dysfunction in diabetic mice,[61] suggesting that these two molecules are relevant therapeutic targets. Inhibition of ROS by overexpression of antioxidant enzymes protects against mitochondrial dysfunction and cardiomyopathy.[13]

Dysregulation of Renin-Angiotensin System

Involvement of the RAAS in the pathogenesis of diabetes-associated HF is increasingly recognized. For example, Ang II has diverse and widespread actions that affect cardiac function.[62] Ang II also exerts actions on other insulin-sensitive tissues, such as liver, skeletal muscle, and adipose tissue, where it has effects on the insulin receptor (IR), IRS proteins, and the downstream effectors PI3K, Akt, and GLUT-4.[63] Underlying molecular mechanisms have not been elucidated definitively, but phosphorylation of both the IR and IRS-1 proteins contributing to desensitization of insulin action is well established.[63] Ang II also has direct effects on cardiomyocytes and cardiac fibroblasts through AT1 receptors, promoting cardiac hypertrophy and fibrosis.[64] Up-regulation of the RAAS has also been described in diabetes and is associated with development of cardiac hypertrophy and fibrosis.[65,66] Furthermore, cardiac dysfunction in diabetes can be mitigated by pharmacologic inhibition of the RAAS.[46] In addition, cardiomyocytes and endothelial cells in the hearts of individuals with diabetes and end-stage HF manifest evidence of oxidative stress, apoptosis, and necrosis that correlate with RAAS activation.[67,68]

Emerging Modulators of Insulin Signaling and Cardiac Function

Adipokines

Historically, adipose tissue has been viewed largely as a repository for surplus lipids, available for mobilization and use in times of metabolic need. It is now recognized that adipocytes synthesize and secrete a number of cytokines (adipokines) that play significant roles in type 2 diabetes and insulin resistance and interact with most organs in the body. Studies to date have focused on the effects of adipokines in promoting or retarding progression from metabolic syndrome to overt T2DM. However, the effects of long-term exposure to circulating adipokines in diabetes warrant further exploration.

Leptin

The hormone leptin is largely involved in regulating food intake, via actions in the central nervous system and peripheral tissues. However, despite extensive investigation into the role of leptin in diabetic cardiomyopathy, controversy persists.[69] For one, leptin has been thought to exert largely detrimental effects on the heart, including negative inotropy (mediated by endogenously produced nitric oxide), prohypertrophy (via an autocrine response to endothelin-1 and Ang II stimulation), and decreased cardiac efficiency (mediated by increased FA oxidation and TG hydrolysis).[18] Now, emerging evidence suggests that leptin protects the heart from lipotoxicity and the relatively hypoxic milieu associated with diabetic cardiomyopathy. Administration of exogenous leptin reverses both LV dysfunction and hypertrophy and is associated with improved mortality in leptin-deficient–ob/ob mice after 4 weeks of coronary ligation.[70] Although elevated plasma leptin levels are generally predictors of poor outcome in patients with CAD and HF, leptin may protect against ischemia/reperfusion injury, possibly via ERK1/2 and PI3K-dependent mechanisms.[71] A possible explanation for these apparent contradictions is the complex interplay between the effects of provoking a central, sympathetic response and the peripheral actions of leptin. Unraveling these multifactorial actions will require both cardiac-specific inactivation of leptin receptors and elucidation of the central nervous system effects of leptin.

Adiponectin

Adiponectin is an adipose tissue–derived hormone that circulates at high levels (5 to 10 μg/mL). In both humans and rodents, plasma adiponectin levels correlate positively with insulin sensitivity and inversely with hypertension, hyperlipidemia, and insulin resistance.[72] Adiponectin stimulates beta-oxidation in muscle and suppresses glucose production in liver, which together antagonize the metabolic syndrome and maintain whole body energy homeostasis.[73] Depressed levels of circulating adiponectin have been shown to correlate with elevated risk of myocardial infarction, CAD, and HF.[74] Recently, mechanisms underlying the actions of adiponectin on the cardiovascular system have been uncovered. Shibata and colleagues reported that adiponectin elicits antihypertrophic effects during cardiac remodeling; adiponectin-deficient animals manifest an amplified hypertrophic growth response to surgical thoracic aortic constriction (TAC).[75] Conversely, adenoviral reconstitution of circulating adiponectin restores the typical hypertrophic response to TAC through activation of adenosine monophosphate–activated protein kinase (AMPK).[75] Adiponectin can mitigate ischemia/reperfusion injury to the myocardium through activation of AMPK and cyclooxygenase 2.[76] It is interesting to note that adiponectin has been detected in cardiomyocytes, raising the possibilities of both autocrine and paracrine effects within the myocardium.[77] In addition, recently it has been shown that adiponectin treatment can increase intracellular calcium levels in muscle through the adiponectin receptor 1[78]; however, the function of adiponectin in cardiomyocyte calcium homeostasis remains to be elucidated.

Resistin

Resistin is a 12-kD hormone that circulates as a high-order complex in plasma.[79] Ample evidence from animal studies points to a significant proinflammatory action of resistin to promote insulin resistance in various tissues.[80] Epidemiologic studies have revealed a positive correlation between circulating resistin levels and risk of developing HF.[81] Recent studies suggest that resistin can modulate glucose metabolism, insulin signaling, and contractile performance in the diabetic heart. Resistin has been reported to impair glucose transport in isolated murine cardiomyocytes and to be upregulated by cyclic stretch and aorta-caval shunting in rodent models, suggesting that resistin affects cardiac function.[18] Adenoviral transduction of resistin in neonatal rat cardiomyocytes triggers robust hypertrophy with increased expression of hypertrophic genes.[82] Resistin is also associated with activation of the ERK1/2-p38 MAPK pathways and with increased serine-636 phosphorylation of insulin receptor substrate 1 (IRS 1).[82] Adenoviral induction of resistin in adult myocytes reduces contractility, possibly via reduction in Ca^{2+} transients.[82] It is likely, therefore, that high levels of resistin as observed in diabetes contribute to the impairment of cardiac function, possibly through alterations in cardiac metabolism and induction of myocardial insulin resistance.

UNFOLDED PROTEIN RESPONSE

Up to 35% of cellular proteins are synthesized and assembled in the endoplasmic reticulum (ER).[83] Abnormal protein folding and the accumulation of excessive aberrantly processed molecules have been linked to pathology of various diseases including diabetic cardiomyopathy.

Cells have evolved an elaborate quality control system to ensure that only correctly folded proteins exit the cell.[84] The unfolded protein response (UPR) is an evolutionarily conserved mechanism to cope with and ameliorate stress imposed by misfolded proteins. When misfolded proteins accumulate in the ER lumen, cells react by upregulating molecular chaperones to enhance protein-folding capacity and ER-associated protein degradation to eliminate terminally unfolded molecules. In concert, protein translation is attenuated to decrease the influx of new client molecules in the ER, thereby creating a window-for-repair to reestablish homeostasis. Ultimately, if ER stress persists, the UPR may trigger cell death for the benefit of the organism.[85]

The UPR is governed by three distinct branches of signal transducers (**Fig. 24-4**).[86] When the UPR is triggered, protein kinase RNA–like endoplasmic reticulum kinase (PERK) is activated, which in turn phosphorylates E74-like factor 2alpha (eIF2α). This phosphorylation event, in turn, attenuates the translation initiation activity of eIF2α, thereby decreasing the ER workload. Activation of the second branch, inositol-requiring enzyme 1 (IRE1), stimulates unconventional splicing of X-box binding protein 1 (XBP1) to generate spliced XBP1 (XBP1s). XBP1s acts as a transcription factor to upregulate a host of molecular chaperones to aid folding within the ER. As for the third arm, activating transcription factor 6 (ATF6) is transported to the Golgi apparatus and processed and activated by protease-mediated cleavage. ATF6 then functions as a transcription factor to boost expression of genes coding for ER chaperones.

Accumulating evidence suggests that ER stress is involved in the pathogenesis of diabetic cardiomyopathy. ER stress markers, including binding protein (BiP), C/EBP homologous protein (CHOP), and PERK, are induced in the heart in animal models of diabetes.[87,88] These findings were later confirmed in several in vitro studies using H9c2 cells or neonatal cardiomyocytes in culture.[88] Mechanistically, excessive production of ROS in the diabetic heart causes protein-folding abnormalities in the ER, which leads to the UPR.[61,87,88] Some evidence suggests that antioxidant treatment can ameliorate cardiomyopathy and attenuate ER stress activation, suggesting a direct link between diabetic cardiomyopathy, ROS, and the UPR.[87]

AUTOPHAGY

Autophagy is a self-eating process that serves to sustain cell function in the setting of nutrient deprivation.[89] Basal autophagic activity is indispensable to recycle long-lived proteins and defective organelles. Dysregulation of autophagy has been implicated in various diseases, including cancer, cardiovascular disease, and the metabolic syndrome.[90]

Autophagy is an elegantly controlled and highly dynamic process (**Fig. 24-5**). To date, 32 autophagy-related proteins (ATGs) have been identified; these proteins regulate the

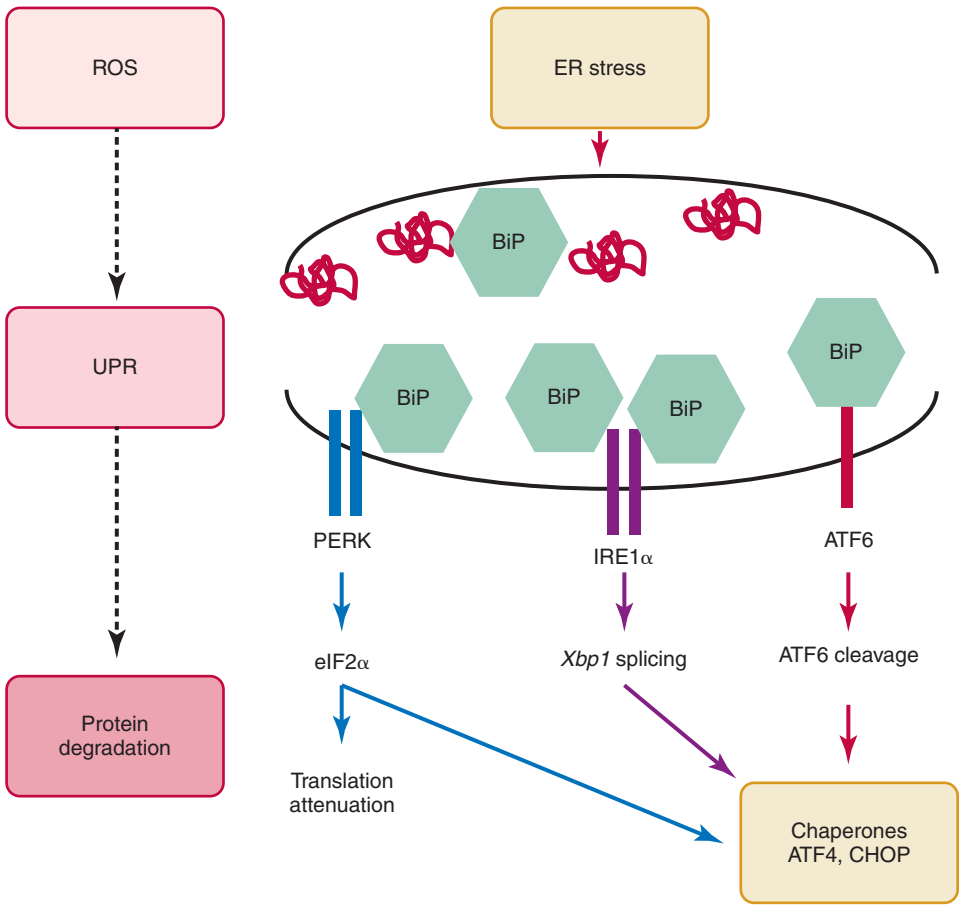


FIGURE 24-4 ER stress response. Schematic representations of three signaling transducers of the ER stress response. Under normal conditions, the ER-resident chaperone BiP (binding protein) interacts with the transducers and prevents their activation. Accumulation of misfolded protein in the ER releases BiP, triggering activation of protein kinase RNA–like endoplasmic reticulum kinase (PERK) and inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6). CHOP = C/EBP homologous protein; eIF2a = eukaryotic initiation factor 2 alpha; Xbp1 = X-box binding protein 1.

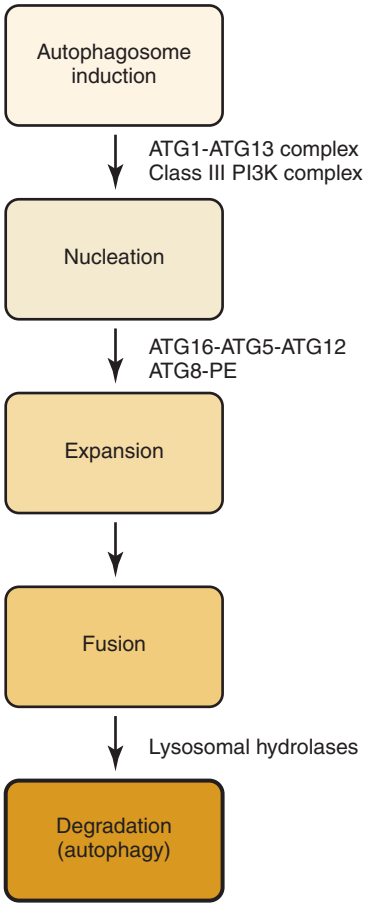


FIGURE 24-5 The autophagic process. Autophagy is an evolutionarily conserved process of intracellular protein and organelle recycling that copes with metabolic and protein-folding stress. A number of autophagy-related genes are involved in this dynamic and tightly regulated process. ATG = Autophagy-related protein; PE = phosphatidylethanolamine.

initiation and progression of autophagy.[91,92] Nutrient deprivation promotes activation of an ATG1-ATG13 kinase complex and formation of the nascent autophagic membrane, the phagophore. The subsequent expansion process is regulated by two ubiquitin-like complexes, ATG5-ATG12 and ATG8-phosphatidylethanolamine. A portion of the cytosol is engulfed within the growing membrane complex, and ultimately a double-membrane structure (autophagosome) is formed. Next, fusion of the autophagosome with a lysosome occurs, leading to hydrolysis of the engulfed contents by lysosomal enzymes. Constituent elements, including amino acids, lipids, and sugars, are released into cytosol for energy production. Finally, ATG9 is involved in retrieval of certain components of autolysosome. Although basal autophagy is essential, excessive autophagic activity has been linked to adverse effects and maladaptive responses.[93]

Autophagy has been implicated in diabetic cardiomyopathy. Early studies found that high-fructose feeding caused cardiac damage in mice, which correlated with significant upregulation of autophagy.[94] However, another study using a different animal model reported opposite findings; autophagy was decreased in diabetic OVE26 mouse hearts.[95] These investigators also showed that metformin significantly improved cardiac function and enhanced the autophagic response in heart.[95] A subsequent study from the same group found that active AMPK can disrupt the Bcl-2–Beclin 1 complex and therefore stimulate autophagy.[96] Although the role of autophagy in diabetic cardiomyopathy remains elusive, current evidence suggests that autophagy plays a role.

CURRENT TREATMENT STRATEGIES AND POTENTIAL THERAPEUTIC TARGETS

Therapy specific to diabetic cardiomyopathy does not exist. However, dissection of the pathophysiology of diabetic cardiomyopathy and disease-related metabolic remodeling in the heart has progressed considerably in recent years. As a result, several novel mechanisms and molecular targets have emerged. The central role of myocyte insulin resistance in the pathogenesis of cardiomyopathy suggests that this signaling cascade is a logical starting point for targeted treatment. For one, lifestyle changes, including diet and exercise, can reduce the incidence of T2DM and improve cardiovascular health.[97] In addition, drugs that enhance glycemic control, such as the antidiabetic drug metformin, which activates AMPK, may confer cardiovascular benefit. AMPK plays a central role in the heart-regulating metabolism and energy homeostasis, and AMPK activation can be cardioprotective during conditions of ischemic stress.[98] Incretin pathway modulators, such as glucagon-like peptide-1 (GLP-1) agonists, have been suggested to be cardioprotective,[99] but whether these effects extend to treatment of diabetic cardiomyopathy is not known. Modulators of free FA metabolism (e.g., perhexiline, trimetazidine, ranolazine, amiodarone), some originally identified as antianginal drugs, have also been suggested to be of potential benefit and may reduce lipotoxicity.[100] Resveratrol, an activator of the NAD-dependent protein deacetylase Sirt1, lowers blood glucose and increases insulin sensitivity,[101] and Sirt1 regulates the activity of FoxO transcription factors.[102] In addition, Sirt1 modulates the activity of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), which is involved in, among other things, mitochondrial biogenesis and function.[102] More potent activators of Sirt1 are currently being developed. Finally, cell-based therapy and genetic correction (through vector-based gene transfer) of abnormalities in cardiac excitation-contraction coupling and insulin signaling are emerging as potential strategies in the treatment of HF.[18]

Forkhead Transcription Factors

FoxO (Forkhead box-containing protein, O subfamily) proteins are emerging as important targets of insulin and other growth factor action in the myocardium.[103,104] Abundant evidence demonstrates that three members of the FoxO subfamily (FoxO1, FoxO3, FoxO4) are critical to maintenance of cardiac function and stress responsiveness.[103,104] FoxO transcription factors regulate cardiac growth and govern insulin signaling and glucose metabolism in heart.[105,106] Furthermore, recent work has implicated chronic activation of FoxOs in the pathogenesis of diabetic cardiomyopathy (**Fig. 24-6**).[25] Specifically, cardiomyocyte-specific inactivation of FoxO1 (FoxO1 KO) rescued high-fat diet (HFD)–induced myocyte hypertrophy and associated declines in cardiac function while preserving cardiomyocyte insulin responsiveness.[25] FoxO1-depleted cardiomyocytes displayed a shift in their metabolic substrate usage from free

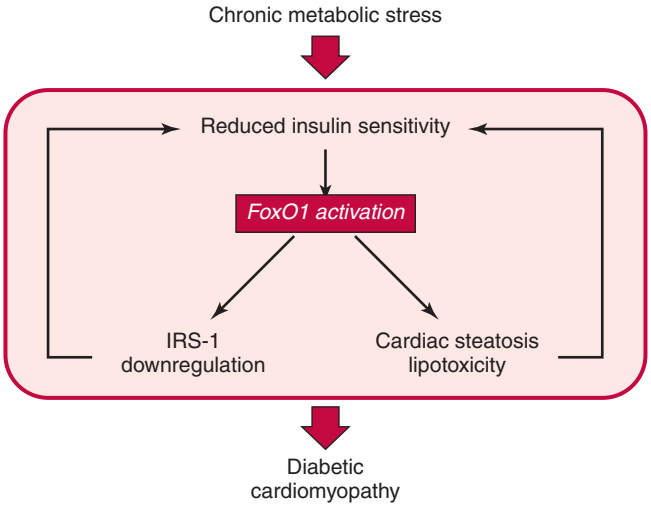


FIGURE 24-6 FoxO1. Hypothesized role of FoxO1 in the pathogenesis of diabetic cardiomyopathy. *(Modified from Battiprolu PK, Hojayev B, Jiang N, et al. Metabolic stress-induced activation of FoxO1 triggers diabetic cardiomyopathy in mice,* J Clin Invest *122:1109-1118, 2012.)*

FAs to glucose, and accumulation of myocardial lipids was reduced.[25] Furthermore, a direct causal link was demonstrated, by which FoxO1-dependent downregulation of IRS-1 resulted in blunted Akt signaling and insulin resistance. Although these findings suggest that activation of FoxO1 is a significant mechanism underlying diabetic cardiomyopathy, an in-depth understanding of specific molecular targets and the transcriptional interplay between FoxO1 and IRS-1 will be required to move this biology toward the clinic.

FoxO has emerged recently as a major mechanism governing insulin signaling and glucose metabolism in a variety of tissues, including liver.[107,108] Chronic activation of hepatic FoxO1 triggers dysregulated expression of a wide array of gluconeogenic genes, events that contribute to systemic insulin resistance.[107,108] It is interesting to note that concomitant liver-specific deletion of both Akt1/2 and FoxO1 in mice restored appropriate adaptation to the fed and fasted states, as well as normal insulin action to suppress hepatic glucose production.[107,108] Moreover, silencing of hepatic FoxO1 largely normalized gluconeogenesis gene expression, lowered the concentration of circulating glucose, and diminished the basal rate of glucose production in insulin-resistant, diabetic mice.[106–108] Thus, inhibition of FoxO1 activity might emerge as a promising strategy to ameliorate features of the metabolic syndrome, such as hyperglycemia, hyperinsulinemia, and insulin resistance.[107] However, the role of FoxO1 in hypertriglyceridemia and hepatic steatosis, which typically accompany insulin resistance and hyperglycemia, warrants further investigation.[107,108] It has also been reported that Notch1 signaling can act in a coordinated manner with FoxO1 to regulate hepatic glucose production, and pharmacologic inhibition of the Notch1 cascade enhanced insulin sensitivity in diet-induced obese mice.[110]

Mammalian Target of Rapamycin

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cell growth and metabolism and is dysregulated in cancer and DM.[111,112] mTOR comprises two multiprotein complexes: mTORC1, which regulates pathways involved in messenger RNA (mRNA) translation and autophagy, and mTORC2, which regulates insulin signaling and other cellular processes. Insulin and IGFs are major mTOR activators that signal through phosphoinositide 3-kinase (PI3K) and Akt.[113] Also, AMPK, which is activated on energy depletion, calorie restriction, or genotoxic damage, has been implicated in stress-responsive inhibition of mTOR.[113,114] mTOR stimulates cell growth and anabolism by increasing protein and lipid synthesis through activation of S6K (p70 ribosomal protein S6 kinase), 4E-BP (eukaryotic translation initiation factor 4E-binding protein), and SREBP (sterol response element binding protein)[113,115,116] and by decreasing autophagic catabolism through inhibition of ATG1.[115] Persistent activation of mTOR has been implicated in diverse pathologies, including cancer and obesity-related metabolic pathologies.[115] Sestrins, another group of conserved stress-responsive proteins, are increased by ROS accumulation, leading to activation of JNKs (c-Jun *N*-terminal kinase) and FoxOs.[117] In contrast, silencing of sestrin resulted in triglyceride accumulation, mitochondrial dysfunction, muscle degeneration, and cardiac dysfunction, suggesting involvement in negative feedback regulation of mTOR.[117]

mTOR, along with other kinases such as JNK, phosphorylate IRS-1 on serine residues, leading ultimately to IRS-1 degradation.[118] Indeed, deletion of mTOR substrates such as S6K1 is sufficient to improve insulin sensitivity and extend lifespan in mice.[119] This suggests that rapamycin, a known inhibitor of mTORC1, might act in a similar manner. Conversely, recent work suggests that chronic treatment with rapamycin impaired, rather than improved, glucose homeostasis.[120] This effect was shown to be mediated by mTORC2 inhibition, provoking insulin resistance and impaired glucose homeostasis potentially by blocking insulin-responsive Akt.[120,121] Thus, modulators of either mTOR (e.g., rapamycin) or the distinct branches of the mTOR signaling cascade and their downstream molecular targets (e.g., growth factor receptor–bound protein 10 [GRB10]),[122,123] are of interest as potential points of therapeutic attack in diabetic heart disease.

MicroRNAs

MicroRNAs (miRNAs or miRs) are naturally occurring, small noncoding single-strand RNAs that regulate gene expression, usually by targeting mRNAs for degradation or by repressing protein translation. In some circumstances, miRNAs upregulate translation of certain mRNAs, especially during cell cycle arrest or in terminally differentiated cells.[124] miRNAs have been identified as important molecular regulators participating in many biologic functions. However, their actions are complex and nuanced, as they target a wide range of transcripts, often in a cluster of processes involved in a given biologic event (e.g., fibrosis, cell death). Furthermore, miRNAs merely fine-tune, as opposed to frankly suppress, the actions of their target mRNAs.

Numerous miRNAs are altered in diabetes.[124–127] For example, miRNAs 103 and 107 (miR-103 and miR-107) are negative regulators of hepatic insulin sensitivity,[129] and both are upregulated in obesity. Silencing miR-103 and miR-107 rescues insulin sensitivity in ob/ob and diet-induced obese mice by affecting adipocyte differentiation.[129] One of the targets for miR-103 and miR-107 is the gene encoding caveolin-1, the major protein of caveolae, the distinctive

lipid- and cholesterol-enriched invaginations of the plasma membrane. Caveolin-1 stabilizes caveolae and their associated IRs, promoting insulin signaling. By reducing caveolin-1 levels, miR-103 and miR-107 alter IR stability and activation.[129] However, whereas both miRNAs are strongly expressed in cardiac and skeletal muscle,[130] their potential role in insulin resistance in the heart remains unknown.

miR-223 is another miRNA that is consistently upregulated in diabetes, including in cardiac tissue.[125] miR-223 expression increases basal glucose uptake in cardiomyocytes, and exposure to insulin does not lead to further increases.[125] This enhanced glucose uptake is caused by elevated expression and preferential plasma membrane translocation of GLUT-4.[125] Because plasma membrane–localized GLUT-4 is markedly downregulated in diabetic hearts,[131] the increase in miR-223 expression in diabetic patients could be an adaptive response to restore glucose uptake.

A recent report demonstrated that the cardiac-specific miR-208a regulates systemic energy homeostasis by targeting MED13, a subunit of the mediator complex that controls transcription by nuclear hormone receptors, including the thyroid hormone receptor.[132] Pharmacologic inhibition of miR-208a or cardiac overexpression of MED13 enhanced metabolic rate, conferred resistance to obesity, improved glucose homeostasis, and lowered plasma lipid levels in mice.[132] Further research will be required to elucidate mechanisms whereby MED13 alters systemic metabolic rate.

Alterations in intracellular calcium handling and impaired SERCA2a activity are cardinal features of the failing heart. Indeed, *SERCA2a* gene therapy in failing hearts improves cardiac function and reduces arrhythmias in vivo.[133,134] It is interesting to note that elevated cytoplasmic calcium concentrations in failing cardiomyocytes promote CaMKK (calcium/calmodulin-dependent protein kinase kinase)–dependent activation of Akt, which in turn inhibits FoxO3a activity, leading to downregulation of miR-1, a FoxO3a target.[135] NCX-1 (sodium-calcium exchanger 1) mRNA is one of the main targets of miR-1, and increases in NCX-1 levels may contribute to calcium mishandling in HF. *SERCA2a* gene therapy restored calcium levels in cardiomyocytes from failing hearts, normalizing Akt and FoxO3a activity and miR-1 and NCX-1 levels.[135] Collectively, these studies raise the prospect that altering miRNA expression may provide novel opportunities for therapeutic intervention in diabetic cardiomyopathy and other cardiac diseases.

Pim-1

In addition to altered calcium homeostasis, downregulation of prosurvival signaling factors has also been implicated in diabetic cardiomyopathy.[136] Pim-1 (proviral integration site for Moloney murine leukemia virus 1) is a serine/threonine protein kinase that modulates SERCA and promotes cardiomyocyte survival and function.[136,137] Pim-1 is upregulated in failing hearts, potentially as an inefficient, last-ditch attempt to preserve cardiac function.[138] It is interesting to note that Pim-1 is downregulated in the initial phase of diabetic cardiomyopathy and continues to decline, leading to severe contractile dysfunction and HF.[136] Furthermore, Pim-1 is positively regulated by STAT3 (signal transducer and activator of transcription 3) and Akt,[137] both of which are downregulated in diabetic cardiomyopathy.[139] Both STAT3 and Akt act as modulators of insulin and nutritional status in the heart.[140] On the other hand, Pim-1 is inactivated by protein phosphatase 2A (PP2A)[141] and is a target of miR-1.[142] It has been proposed that the increased intracellular levels of ceramide in diabetic myocardium may in part explain the upregulation of PP2A,[141] contributing to Pim-1 downregulation.

Pim-1 is also implicated in promotion of cardiomyocyte survival via activation of Bcl2 (B-cell lymphoma 2) and phosphorylation or inhibition of Bcl-2-associated death promoter (BAD) and in the maintenance of mitochondrial integrity.[137,143] Furthermore, Pim-1 increases the proliferative activity of cardiac progenitor cells by inducing c-Myc, nucleostemin, cyclin E expression, and p21 phosphorylation.[144,145] Therefore, it is tempting to speculate that the accrual of alterations in upstream Pim-1 activators[139] and the confounding upregulation of Pim-1 inhibitors, such as PP2A and miR-1, contribute to the unique features observed in hearts of diabetic mice compared with other ischemic and pressure-overload models. In addition, as noted earlier, some work suggests that cardiac-specific *Pim1* gene therapy attenuates the progression of diabetic cardiomyopathy,[136] raising yet further the prospects of targeting this interesting molecule. Finally, it is important to point out that all the studies on Pim-1 have been performed in streptozotocin-treated animals, a model used to mimic late stages of T2DM characterized by insufficient insulin action. Future studies will be required to determine the relevance of Pim-1 in T2DM or metabolic syndromes associated with hyperinsulinemia.

CONCLUSIONS AND PERSPECTIVE

Heart failure has remained a leading cause of death in industrialized nations for some years. Numerous events contribute to the rise in HF, but the increasing prevalence of DM is an important contributor. Derangements in insulin signaling have widespread and devastating effects in numerous tissues, including the cardiovascular system. The multiple, interlacing events occurring in patients with diabetes culminate in an environment that, coupled with insulin resistance, leads to diabetic cardiomyopathy. In recent years, novel insights into mechanisms that increase vulnerability of the diabetic heart to failure have emerged. Functional consequences, including diastolic dysfunction, systolic dysfunction, fibrosis, and ultimately clinical HF, correlate with glycemic control. These organ-level functional alterations are preceded by a complex array of molecular and cellular changes, many of which are present in asymptomatic diabetic individuals and experimental models of diabetes. Despite emergence of these insights, our understanding of diabetic cardiomyopathy—a disease that is at once intricate and clinically significant—remains rudimentary.

Constant and unremitting metabolic stress on the heart leads over time to progressive deterioration of myocardial structure and function. This suggests that therapeutic interventions early in the disease, targeting specific metabolic and structural derangements, may be required. This is especially relevant because rigid control of hyperglycemia, however central to treatment, has not fulfilled hopes of meaningful morbidity and mortality benefit.[6] Recent and ongoing research into mechanisms of metabolic control, insulin resistance, and diabetes-associated derangements portend novel therapies designed to benefit the rapidly expanding cohort of patients with diabetes. Continued

efforts to identify effective preventive strategies and treatments are essential. At the same time, there remains a growing need to identify therapies that slow, arrest, or even reverse disease progression, and ongoing research efforts suggest that such may emerge with time.

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25 Prevention of Heart Failure in Patients with Diabetes

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Chronic heart failure (HF) is increasing in prevalence, affecting over 5 million patients in the United States, and it is estimated that more than 20 million individuals have HF globally.[1,2] An ageing population, improved survival after myocardial infarction (MI), and a rising incidence of noncommunicable diseases such as hypertension and diabetes in developing economies have all contributed to the increased disease burden worldwide. Although studies show progress in evidence-based treatment for HF with systolic dysfunction, it often remains a progressive condition and is associated with high mortality risk.[1] In particular, these treatments are often instituted fairly late in the disease course when patients are symptomatic with significant LV dysfunction, and its impact on overall survival may be modest on a population basis. Furthermore, there have been no major discoveries in therapeutic options for patients with HF with preserved ejection fraction (HFpEF), a condition that often coexists with a diagnosis of diabetes mellitus, especially among older women. Given the irreversible nature of late-stage HF syndromes, prevention and early detection of HF should be priorities. Largely, the prevention of HF is targeted at identifying the associated risk factors for its development and intervening, especially when multiple risk factors combine, increasing the risk of both HF and its subsequent sequelae.

Diabetes has long been associated with increased risk of incident HF (see **Chapter 23**).[3–5] Longitudinal epidemiologic studies, such as the Framingham Heart Study, have shown that diabetes increases the lifetime risk of developing symptomatic HF by 2.4-fold in men and 5.0-fold in women, independent of coexisting hypertension or coronary artery disease.[5] Furthermore, higher hemoglobin A1c (HbA1c) levels are associated with an incrementally greater risk for development of HF.[6–9] Therefore, patients diagnosed with diabetes represent a critical target population for early detection and prevention of HF. In view of the poor prognosis associated with the diagnosis of HF, its prevention should be undertaken with the same seriousness as prevention of other cardiovascular (CV) complications in patients with diabetes. In this chapter we address the strategies and challenges of preventing and screening for HF among patients with diabetes and diabetes management in patients at risk of developing HF.

STRATEGIES FOR PREVENTION OF HEART FAILURE

The fundamental principle of effective preventive strategies is to be able to reliably detect individuals who are at risk of developing a disease or who exhibit evidence of pathologic processes capable of causing progression to clinical disease state. Effective interventions should reduce the risk of progression to disease, significantly delay the clinical onset of disease, or alter the trajectory of disease progression. In addition, the condition targeted by preventive strategies should carry significant morbidity and mortality risks that need to be balanced against the resources required and potential risks that may be associated either with the screening process or with any preemptive treatment. For achievement of these goals, a thorough understanding of the prevalence and natural history of both the risk factors and the disease state is crucial.

IDENTIFYING PRECURSORS OF SYMPTOMATIC HEART FAILURE

HF is a progressive disorder. Despite the heterogeneity of the etiology of HF, LV dysfunction begins in individuals with risk factors that contribute to insults to or persistent stress on the myocardium (see **Chapter 24**), which may remain asymptomatic in a significant proportion of individuals. The resultant maladaptive changes in the LV geometry (remodeling) and neurohormonal activation culminate in a failing heart, with patients experiencing dyspnea, congestion, and decreased exercise tolerance; requiring repeated hospitalizations; and having increased mortality risk. Recognizing the importance of prevention in addressing the rising prevalence of HF, international professional guidelines and scientific statements have highlighted the need for aggressive risk modification among individuals at risk of developing HF. The American College of Cardiology (ACC) and the American Heart Association (AHA) introduced an HF classification based on stages of risk and development and progression of HF.[10] The classification includes individuals with risk factors associated with increased risk of developing clinical HF without evidence of structural heart

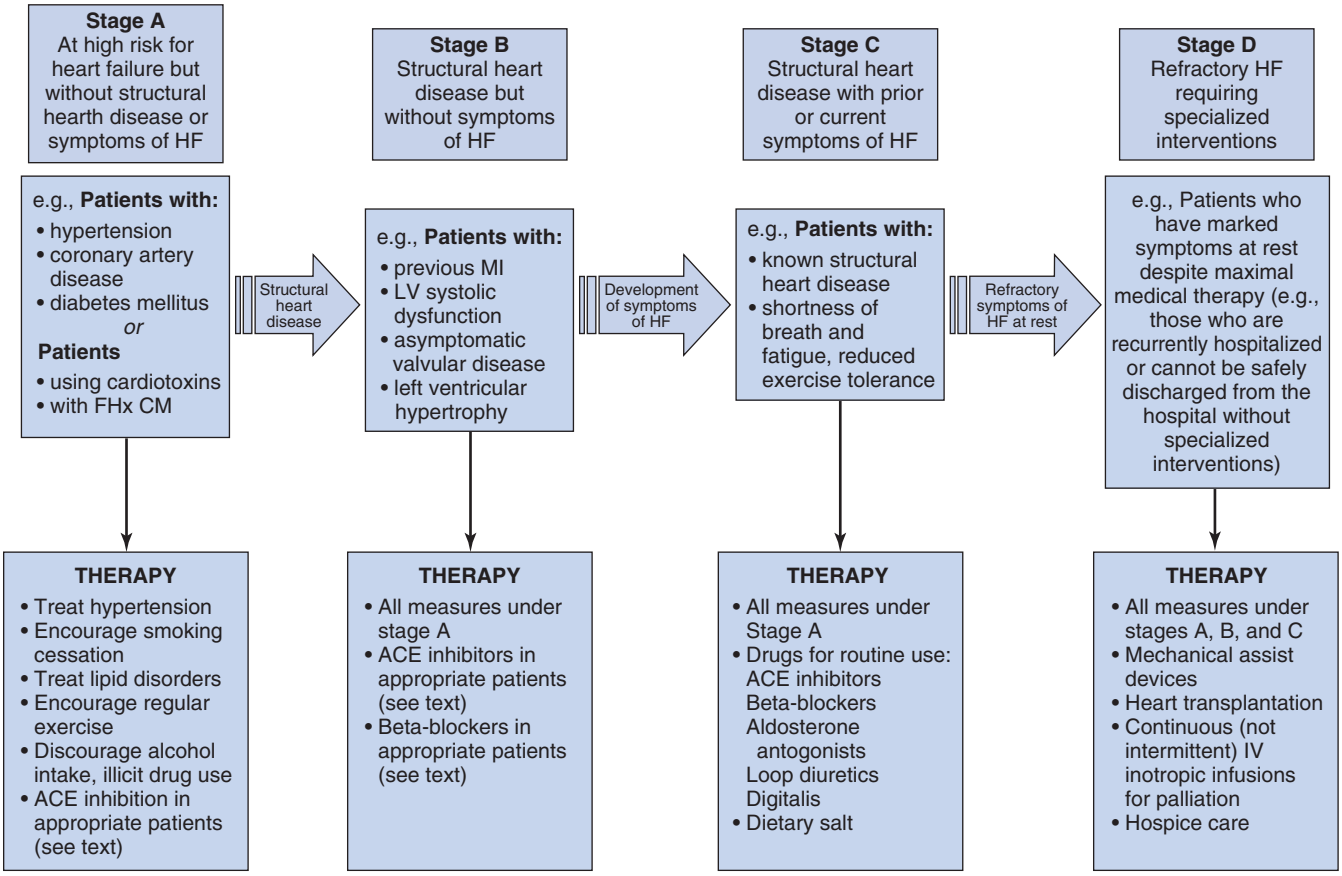


FIGURE 25-1 ACC/AHA stages of HF evolution and recommended therapy. ACE = Angiotensin-converting enzyme; FHx CM = family history of cardiomyopathy; IV = intravenous; MI = myocardial infarction. *(Modified from Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure]: developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America,* Circulation *104:2996-3007, 2001.)*

disease (stage A), patients with structural heart disease but without overt clinical symptoms (stage B), patients with clinical HF syndromes with either current or past HF symptoms (stage C); and patients with end-stage refractory HF (stage D) (**Fig. 25-1**). By incorporating those who are at increased risk for HF but do not exhibit HF symptoms (stages A and B), but who are nevertheless at significant risk of progressing to irreversible cardiac dysfunction, the ACC/AHA classification highlighted the need to target these "pre-HF" patients for preventive measures with the aim of altering the natural history progression.

Stage A Heart Failure

Among patients with diabetes, coexisting risk factors for HF such as atherosclerotic diseases, hypertension, and obesity increase the risk of developing subsequent LV dysfunction. These risk factors are highly prevalent among patients with diabetes and represent an important clustering of modifiable risk factors to consider for population-targeted intensive risk factor intervention for HF prevention. From population studies, the prevalence of stage A HF among individuals aged 45 years or older is approximately 20%.[11] The underlying assumption is that by aggressively treating these modifiable risk factors underpinning the hazard for HF, the risk of progression to overt LV dysfunction could be mitigated. As these CV risk factors often coexist and contribute to other diabetes CV complications, lifestyle modification and pharmacologic treatments aimed at treating such risk factors may lead to multifaceted CV risk reduction, including but extending beyond risk for HF.

Stage B Heart Failure

Stage B heart failure refers to structural and functional cardiac abnormalities without overt clinical manifestations of HF, based predominantly on cardiac imaging results. For practical purposes, it has been narrowly defined as previous MI with regional dysfunction or scar, left ventricular hypertrophy (LVH), left ventricular systolic dysfunction (LVSD; or reduced ejection fraction [EF]), or structural valve disease. Based on data from cross-sectional population studies, stage B HF is estimated to affect approximately one third of the population 45 years of age or older.[11] The magnitude of this at-risk group suggests that a significant proportion of the population may benefit from early identification of abnormal LV structure and function so that preventive interventions may be applied most efficiently. This is also an important group to target for clinical trials of early pharmacologic intervention for systolic and diastolic dysfunction.

Among the subcategories of stage B HF, LVSD has been the most studied. Depending on the age of the population studied and the EF threshold chosen to characterize abnormal LV function, the prevalence of asymptomatic LVSD in

BOX 25-1 Risk Factors Associated with Increased Risk of Heart Failure (HF) in Diabetic Patients Treated with Thiazolidinediones (TZDs)

- History of HF (either systolic or diastolic)
- History of prior MI or symptomatic coronary artery disease
- Hypertension
- LVH
- Significant aortic or mitral valve heart disease
- Advanced age (>70 years)
- Longstanding diabetes (>10 years)
- Preexisting edema or current treatment with loop diuretics
- Development of edema or weight gain on TZD therapy
- Insulin coadministration
- Chronic renal failure (creatinine >2.0 mg/dL)

Data from Nesto RW, Bell D, Bonow RO, et al: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003, *Circulation* 108:2941-2948, 2003.

predominantly middle-aged and elderly adults ranges from 2% to 10%, with higher rates reported among men and older adults (**Box 25-1**).[11–20] Asymptomatic LVSD is associated with markedly increased risk of developing clinical HF and is associated with higher mortality risk compared with patients having similar risk factor profiles but without evidence of LVSD. In the Framingham cohort, 26% of participants with asymptomatic LVSD progressed to symptomatic HF during the 5-year follow-up, representing an approximately fivefold increased risk compared with subjects with normal LV function.[13] This was associated with a 60% higher mortality risk, but, more important, over half of the deaths occurred before symptomatic HF developed.[13] Although most studies examining the risk of stage B HF progressing to symptomatic HF have included predominantly older white individuals, in a large cohort of white and black young adults (18 to 30 years old at baseline), the presence of asymptomatic LVSD was a strong predictor of incident HF (greater than 30 times the rate compared with individuals with normal EF) before the age of 50 years, independent of other clinical risk factors, including blood pressure (BP).[21] Given the irrefutable evidence suggesting stage B HF as a precursor to symptomatic HF and its associated risk of mortality, targeting diabetic patients with stage B HF for aggressive preventive measures may meaningfully modify the trajectory of the disease progression into symptomatic HF.

SCREENING STRATEGIES FOR PREVENTION OF HEART FAILURE

The first step of any HF preventive strategy is to identify the patient population at risk of developing symptomatic HF. Screening may be achieved by using established clinical risk markers as mentioned earlier, complemented by biomarker- and imaging-based approaches to identify patients with subclinical abnormal cardiac structure or function on a progressive path of developing symptomatic HF. Through identification of these at-risk individuals, interventions aimed to modify and reduce the risk of development of clinical HF may be implemented and objectively assessed to determine if a given preventive strategy leads to improved outcomes.

Screening with Clinical Risk Factors

As described, several well-established clinical risk factors, including the diagnosis of diabetes, increase the risk of incident HF and should be used by clinicians to identify those at-risk patients who will benefit from aggressive risk factor modification and primary prevention. Advantages of this strategy are their broad availability and generalized feasibility for clinicians even in areas of limited health care resources. Nevertheless, despite the well-documented association of individual risk factors for HF, quantifying the magnitude of risk for an individual patient in the presence of multiple risk markers may be challenging. Validated HF risk scores, such as those derived from the Framingham Heart Study and the Health, Aging, and Body Composition (Health ABC) Study, allow both clinicians and researchers to systematically risk-stratify patients into various risk levels for development of overt HF.[22–24] Although these risk scores are not specific for patients with diabetes, diabetes and elevated fasting blood glucose have been consistently found to be independent predictors for incident HF. In addition, increased risk of HF identified by the risk scores is associated with subclinical cardiac structural and functional alterations that may lead to overt HF. Among adults 30 to 65 years old, observations from the population-based Dallas Heart Study demonstrated that the prevalence and severity of increased LV mass, LVH concentric remodeling, and LVSD identified with cardiac magnetic resonance imaging (cMRI) incrementally increased across the risk strata defined by the Health ABC risk scores.[25] These observations provided some pathophysiologic underpinnings to support the use of risk scores for identification of individuals at increased risk of incident HF.

Several limitations exist with regard to use of risk prediction scores as a screening strategy. The risk scores mentioned earlier were derived from population studies with either predominantly white participants (Framingham Heart Study) or only white and black participants (Health ABC study), and both studies included only individuals from the United States. This may limit the generalizability of these risk scores in other populations. There also remains a lack of validated risk scores derived specifically from patients with diabetes. Furthermore, despite the availability and validity of these risk scores, in practice appropriate risk stratification and implementation of risk modification interventions are often suboptimal during routine clinical encounters. Recent data from the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2010 showed that although achievement of recommended treatments goals for HbA1c, BP, and low-density lipoprotein cholesterol (LDL-C) among patients with diabetes has improved during the last decade, there remains significant room for further optimization (**Fig. 25-2**).[26] Therefore, there clearly remains an unmet need to effectively translate risk prediction model results into a clinical tool to further advance efforts in prevention of HF through aggressive management of these risk factors. One potential direction is to capitalize on the evolution of integrated health systems and the increasing use of electronic health data, whereby an automated analysis and summary of documented risk elements yielding an estimation of risk could be included in the patient care fields to allow for continuous screening for risk and assessment of efficacy of relevant interventions. Such a process could also generate clinical alerts to inform screening and therapeutic modifications. (See also **Chapter 31**.)

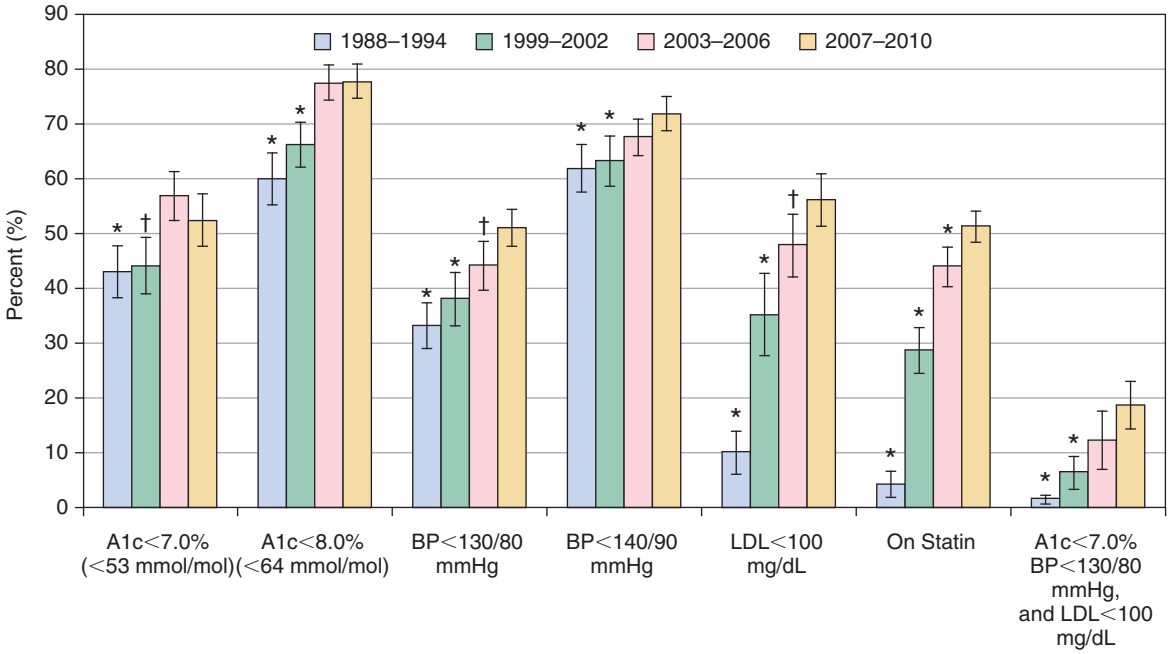


FIGURE 25-2 Prevalence of meeting Health ABC goals among adults aged 20 years of age or older with diagnosed diabetes, NHANES 1988 to 2010. Estimates are age and gender standardized to the 2007 to 2010 NHANES population with diabetes. *$P<0.01$, estimates are compared with those of 2007 to 2010. †$P<0.05$, estimates are compared with those of 2007 to 2010. LDL = Low-density lipoprotein. *(Modified from Stark Casagrande S, Fradkin JE, Saydah SH, et al: The prevalence of meeting A1c, blood pressure, and LDL goals among people with diabetes, 1988-2010.* Diabetes Care *36:2271-2279, 2013.)*

Screening with Biomarkers

In theory, biomarkers are biologic variables that are capable of providing information about the presence, severity, and prognosis of a condition of interest. In practice, the term *biomarker* in HF is limited to circulating serum and plasma analytes that reflect various aspects of the pathophysiology of HF beyond routine hematology and biochemistry panels. To be clinically useful, a particular biomarker must be shown to provide additional information that may alter clinical decision making or guide interventions, above and beyond careful clinical assessment.

Natriuretic Peptides

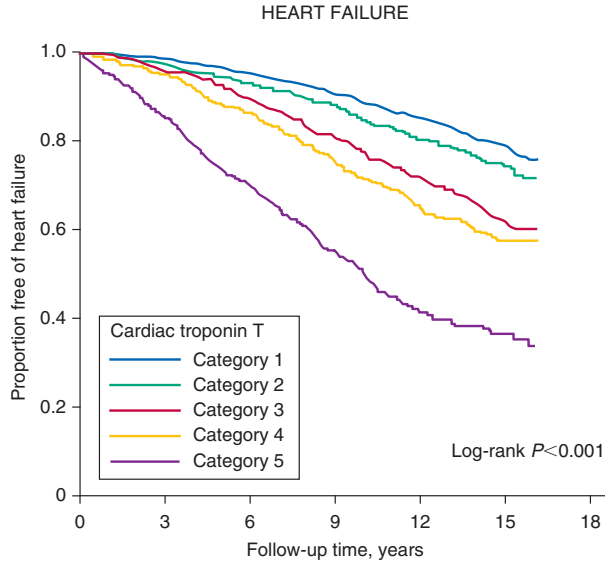
Circulating levels of biologically active brain natriuretic peptide (BNP) and its biologically inert precursor N-terminal peptide (NT-proBNP) are elevated in response to high ventricular filling pressure and have been well established as important diagnostic and prognostic biomarkers among patients with signs and symptoms of overt HF. The success observed demonstrating their value in the clinical context of symptomatic HF has prompted interest in evaluation of these biomarkers as screening tools for HF risk. In population studies and in cohorts with stage A or B HF, the addition of either NT-proBNP or BNP measurements helps refine the predictive capability of traditional clinical risk factors in predicting risk for incident HF hospitalization and mortality, especially in patients with diabetes.[24,27–29] Furthermore, in population studies that included cardiac imaging, the combination of a high clinical risk score and an elevated BNP or NT-proBNP had the ideal predictive characteristics to detect subclinical LVSD, LVH, and diastolic dysfunction.[30,31] Whether the improved risk prediction and stratification may alter management strategies, and in turn improve patient outcomes, remains uncertain. Recent data suggest that a refined HF risk assessment with the use of NT-proBNP and clinical risk factors in conjunction with multifaceted collaborative clinical care may potentially reduce the incidence of clinical HF. The St. Vincent's Screening to Prevent Heart Failure (STOP-HF) study was designed as a pragmatic, prospective randomized trial to examine the efficacy of a screening program using BNP and collaborative care in an at-risk population in reducing newly diagnosed HF and prevalence of stage B HF. The study found that patients randomized to the intervention arm (BNP screening and collaborative care) had a lower incidence of LV dysfunction with or without overt HF (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.37-0.82; $P=0.003$). This may be mediated by better-coordinated care, increased emphasis on adherence to guideline-recommended treatments and healthy lifestyle behaviors, higher rate of screening echocardiography, and significantly more prescription of renin-angiotensin-aldosterone system (RAAS)–based therapy. Nevertheless, the proportion of patients with diabetes in the study was relatively low (less than 20%). Furthermore, the event rate in the STOP-HF study was relatively low, and whether the lower rate of HF diagnosis will indeed translate to improved clinical outcomes in the long term compared with standard care practice remains to be determined.

Cardiac Troponin

Cardiac troponins are key sarcomeric proteins responsible for the contractile function of cardiac myocytes. Detectable circulating levels, a marker of myocyte necrosis, have long been used in the diagnosis and prognostication of acute coronary syndromes,[32–35] myocarditis,[36] and HF.[37–39] The specificity of cardiac troponin as a biomarker for myocardial necrosis underpins its demonstrated adjunctive usefulness when added to clinical risk factors for risk-stratifying apparently healthy individuals to discriminate those at highest risk of developing HF.[40–43] Moreover, newer generations of

cardiac troponin assays with markedly improved detection sensitivity have resulted in much larger proportions of cohorts tested having detectable levels, allowing analysis of their association with subclinical CV pathology and subsequent CV risk across the spectrum of circulating concentrations. For example, in the multiethnic, population-based Dallas Heart Study, detectable levels of high-sensitivity cardiac troponin T (hs-cTnT; lower detection limit 0.003 ng/mL) were associated with increased LVH and left ventricular end-diastolic volume (LVEDV) and modestly reduced left ventricular ejection fraction (LVEF) identified with cMRI.[40] Higher levels of hs-cTnT were also associated with increased risk of subsequent all-cause mortality from 1.9% (95% CI 1.5%- 2.6%) to 28.4% (95% CI 21.0%-37.8%) across incrementally higher quartiles of hs-cTnT levels ($P<0.001$) during a median follow-up of 6.4 years.[40] In a separate population-based study focused on older individuals (65 years or older), higher levels of baseline hs-cTnT levels and changes in cTnT levels were significantly associated with incident HF and CV death (**Fig. 25-3**).[43] Although the overall predictive value of troponins is independent of the presence of diabetes, the magnitude of the incremental value of troponins in predicting incident HF among patients with diabetes is less defined.[44]

Because different biomarkers may reflect specific and different pathophysiologic pathways contributing to myocardial damage, incorporating multiple such biomarkers in risk prediction models may further improve risk prediction beyond that obtained using individual biomarker predictors.[45–47] Before such strategies can easily be incorporated into practice, more data on the cost-effectiveness and the impact of biomarker-based screening strategies on clinical outcomes will be needed.



No. at risk

Category 1	1427	1380	1281	1131	956	763	461
Category 2	697	658	586	508	401	291	169
Category 3	700	642	550	435	333	231	131
Category 4	697	628	505	377	272	176	99
Category 5	700	532	357	213	119	77	36

FIGURE 25-3 Association of serial measures of cTnT using a sensitive assay with incident HF in older adults. Categories of cTnT concentrations were divided into category 1 (<3.00 pg/mL), category 2 (3.00 to 5.44 pg/mL), category 3 (5.45 to 8.16 pg/mL), category 4 (8.17 to 12.94 pg/mL), and category 5 (>12.94 pg/mL). *(Modified from deFilippi CR, de Lemos JA, Christenson RH, et al: Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults,* JAMA *304:2494-2502, 2010.)*

Screening with Imaging

In the era of multimodality CV imaging, detecting LV systolic or diastolic dysfunction can be easily achieved with high precision. Conventional two-dimensional (2-D) or newer three-dimensional (3-D) echocardiography, cMRI, computed tomography (CT) coronary angiography with left ventriculography, and radionuclide imaging could be used to determine LV function, evaluate for the presence of obstructive coronary artery disease (CAD), determine the extent of viable myocardium, and evaluate dyssynchronous LV contraction, either as stand-alone modalities or in combination with complementary imaging techniques. Despite the technologic advances, it remains unclear if imaging-guided screening would further optimize primary prevention of HF or be cost-effective. In the Cardiovascular Health Study (CHS), a multicenter prospective observational cohort study, researchers found that of the 4137 participants without prevalent HF, 107 (2.6%) had subnormal LVEF (<45%) and 210 (5.1%) had a borderline reduced LVEF (45% to 54%) determined with baseline 2-D echocardiography. Although abnormal LVEF (<55%) was associated with increased CV mortality independent of clinical factors and NT-proBNP level, the LVEF did not provide significant incremental predictive value for incident HF when added to NT-proBNP levels and traditional clinical risk factors.[48] These findings, together with the low prevalence of asymptomatic LVSD observed in the general adult population (2% to 10%),[11–20,49] do not support the rationale of using conventional CV imaging modalities as a primary screening tool to identify those at risk of clinical HF. Furthermore, some of these modalities carry significant radiation exposure (e.g., CT and radionuclide scans) and costs (e.g., magnetic resonance imaging [MRI] and single photon emission computed tomography [SPECT]), hence limiting their usefulness as general screening tools. Preselection of a small higher-risk subset based on clinical and biomarker risk markers may improve the yield of an imaging-based screening program, but its effectiveness on improving outcomes would need to be studied.

STRATEGIES FOR RISK MODIFICATION

The ultimate goal of primary prevention of HF in patients with diabetes is to minimize adverse cardiac remodeling by reducing the risk of myocardial necrosis or stressors. This can be achieved by directly addressing prevalent risk factors among patients with diabetes such as coronary heart disease (CHD), hypertension, dyslipidemia, and obesity. Specific pharmacologic agents indicated for other diabetes microvascular and macrovascular complications might offer parallel reduction in the risk of incident HF, in addition to their primary indications. Direct evidence on the efficacy and cost-effectiveness of HF preventive measures is lacking, with most current recommendations based on either (1) observational data on associations of certain risk factors with risk of HF; or (2) secondary endpoints of randomized controlled trials in which incident HF was inconsistently measured and which often lacked adequate statistical power to detect true efficacy. Finally, special considerations regarding the diabetes treatment regimens of patients at risk of developing HF are warranted and are briefly reviewed here.

Coronary Heart Disease and Diabetes

CHD remains the most important risk factor for incident HF among patients with diabetes (see **Chapter 7**). Compared with their nondiabetic counterparts, patients with diabetes are more likely to have CHD and to have multivessel disease when CHD is present, are at increased risk of silent myocardial ischemia, have more microvascular cardiac ischemia, and are at increased risk of restenosis after revascularization procedures. All these factors contribute to higher risks for and increased severity of MI, which in turn increases the risk of post-MI LVSD and downstream HF. Therefore, comprehensive and aggressive management, which includes pharmacologic treatments and lifestyle modifications, of this prevalent comorbidity is key to effectively reduce the risks of developing overt HF.

Despite advances in treatment of acute MI in recent decades, it remains an important cause of clinical HF, especially among patients with diabetes. However, with the exception of the intensity of antithrombotic therapies (see **Chapters 16** and **21**) and choice of coronary stents in percutaneous revascularization (see **Chapter 17**), the management of patients with acute MI is largely similar regardless of the diagnosis of diabetes (see **Chapters 20**, **21**, and **22**).

Post–Myocardial Infarction Prevention of Heart Failure

In addition to the initial ischemic insult caused by an episode of acute MI, patients with diabetes are at risk of recurrent ischemic events, which will gradually deplete the remaining functional myocytes and lead to ongoing adverse remodeling and neurohormonal activation with the resultant increased risk of progression to HF. Therapies aimed at reducing post-MI adverse remodeling and future MIs will likely lead to lower risk of HF development.

The RAAS is activated immediately after MI. Angiotensin II plays a key role in early remodeling of the infarct area and mediates fibrosis via aldosterone and other fibrotic pathway mediators such as transforming growth factor beta (TGF-β), connective tissue growth factor, and tissue inhibitor of matrix metalloproteinase 1 (MMP-1). One of the first studies to demonstrate a cardiac protective effect of angiotensin-converting enzyme (ACE) inhibitors in post-MI patients with LVSD was the Survival and Ventricular Enlargement (SAVE) trial.[50] This study showed that long-term administration of captopril in post-MI patients with LVEF below 40% was associated with significant reduction in all-cause mortality, risk of recurrent MI, and incidence of severe HF (relative risk reduction 34%).[50] In a subgroup analysis, the point estimate of risk reduction among patients with diabetes was consistent with the findings of the main study. However, because of the relatively smaller sample size of the diabetes subgroup and the lack of statistical power based on few events, the treatment difference within the diabetes subset was not statistically significant.[50,51] This finding was confirmed by the Studies of Left Ventricular Dysfunction prevention trial (SOLVD-Prevention), which enrolled 4228 patients with an LVEF below 35%, of whom 83% had had an MI more than 30 days from entry. The study showed that treatment with enalapril (up to 20 mg once per day) significantly reduced the incidence of progression to overt HF and the rate of related hospitalizations.[52] In the echocardiography substudy of the SOLVD-Prevention trial, enalapril was associated with less LV dilation and LVH in patients with stage B HF.[53] Similarly, subgroup analysis of the SOLVD-Prevention study showed that the presence of diabetes was associated with an adverse prognosis; however, the treatment effect of enalapril and its impact on incident HF were similar across the risk profile of patients, which included those with diabetes.[54] In congruence with other studies, the TRACE study showed that treatment with trandolapril in the subset of enrolled patients with diabetes (237 of 1749 patients [14%]) was associated with lower risk of progression to severe HF (relative risk 0.38; 95% CI 0.21-0.67), but no significant reduction of this endpoint was seen in the nondiabetic group.[55] Similarly, in the GISSI-3 trial, treatment with lisinopril versus placebo was evaluated in patients with acute MI; the magnitude of relative risk reduction for all-cause mortality at 6 weeks favoring lisinopril was greatest in the subset of patients with versus without diabetes (**Fig. 25-4**).[56]

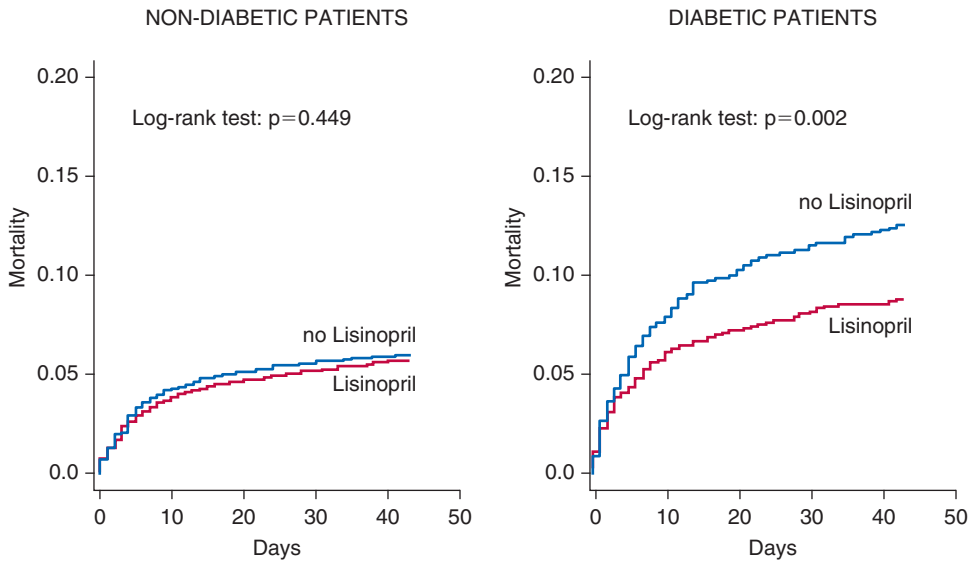


FIGURE 25-4 Differential effects of lisinopril compared with placebo on all-cause mortality in patients with or without diabetes mellitus. *(Modified from Zuanetti G, Latini R, Maggioni AP, et al: Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study,* Circulation *96:4239-4245, 1997.)*

In contrast, treatment with lisinopril versus placebo was not statistically different in either subgroup stratified by diabetes status for the combined endpoint of mortality and LV dysfunction morbidity (defined as [1] clinical HF, [2] asymptomatic LVEF of 35% or lower, or [3] LVEF above 35% but with 45% or more injured myocardial segments evaluated with 2-D echocardiography)—with diabetes, 21.6% versus 24.5% (OR 0.85, 95% CI 0.71-1.01); and without diabetes, 14.3% versus 15.5% (OR 0.91; 95% CI 0.83-1.00). The apparent paradox as compared with the primary endpoint of mortality could be explained by the lower mortality during the acute phase in patients treated with lisinopril, which consequently led to a remnant burden of morbidity for post-MI LVSD among survivors (**Fig. 25-5**).

Hypertension

Hypertension often coexists with diabetes and visceral adiposity and represents a major risk factor for both macrovascular and microvascular complications, including increased risk of incident HF among patients with diabetes. Untreated hypertension accelerates the progression of atherosclerosis, and chronic pressure overload leads to maladaptive LVH, diastolic dysfunction, and subendocardial ischemia caused by impaired microvascular perfusion, and in some patients LVSD ensues. Therefore, appropriate hypertension management is a key treatment goal in improving the overall clinical outcomes of patients with diabetes and specifically preventing progression to HF. (See also **Chapter 14**.)

The United Kingdom Prospective Diabetes Study (UKPDS) compared more intensive BP control (<150/85 mm Hg) with lesser control of BP (<180/105 mm Hg) in 1148 patients with newly diagnosed type 2 diabetes and hypertension.[57] Over a median follow-up period of approximately 10 years, more intensive BP control decreased the risk of developing HF (hazard ratio 0.44; 95% CI 0.2-0.94, $P=0.043$). The UKPDS also demonstrated that captopril and atenolol were comparably efficacious in reducing the risk of HF and other diabetes-related complications.

The role of the angiotensin receptor blocker (ARB) losartan in reducing the risk of incident HF hospitalization among patients with diabetes has been reported from analyses of the patients with diabetes enrolled in two randomized trials: (1) diabetic cohort of the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial, which enrolled patients with hypertension and LVH,[58,59] and (2) the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial of patients with diabetic nephropathy.[58,60] Although the RENAAL trial targeted enrollment of patients with nephropathy and not hypertension specifically, the baseline mean systolic BP was 153 mm Hg.[60] In both trials, losartan was associated with significantly lower incidence of first HF hospitalization, versus placebo in the RENAAL trial (39.3% versus 53.5%; HR 0.74, $P=0.037$) and versus atenolol in the LIFE trial (10.6% versus 18.7%; Hazard ratio [HR] 0.57, $P=0.019$) (**Fig. 25-6**).[58]

Despite the benefits associated with treatment of hypertension in patients with diabetes, the ideal target BP remains debatable (see also **Chapter 14**). Most recent management guidelines recommend that the goal BP be less than 140/90 mm Hg,[61,62] although others advocate a lower target of 130/80 mm Hg in selected patients.[63] Specific treatment goals for patients at risk of HF should be considered for the purpose of minimizing incident HF and should be individualized based on the presence of comorbidities, such as atherosclerosis or nephropathy (proteinuria), and the individual patient's ability to tolerate the antihypertensive without significant adverse effects.

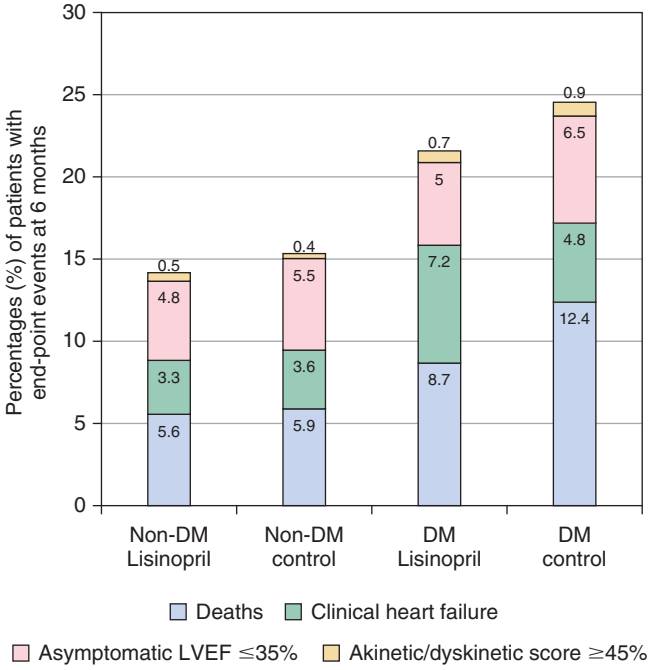


FIGURE 25-5 Effect of the ACE inhibitor lisinopril on mortality and secondary endpoints in diabetic (DM) and nondiabetic (non-DM) patients with acute MI at 6 months follow-up. *(Modified from Zuanetti G, Latini R, Maggioni AP, et al: Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study,* Circulation *96:4239-4245, 1997.)*

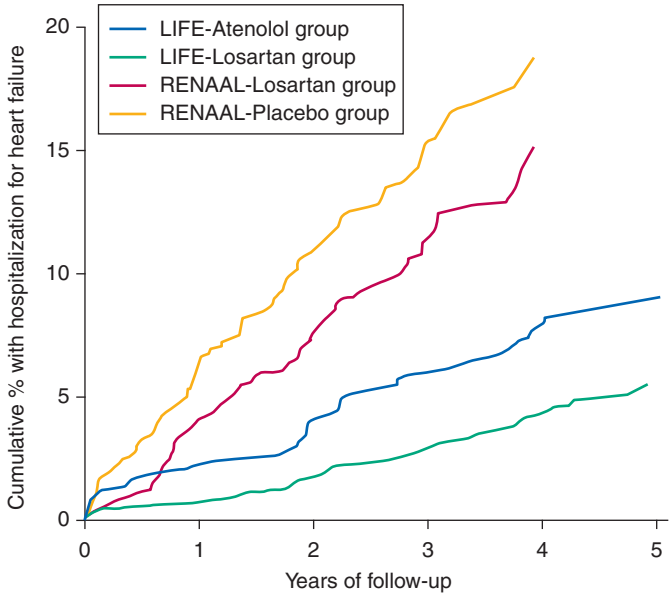


FIGURE 25-6 Incidence of first HF hospitalization in the RENAAL trial (losartan versus control) and the diabetic cohort of the LIFE trial (losartan versus atenolol). *(Modified from Carr AA, Kowey PR, Devereux RB, et al: Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies,* Am J Cardiol *96:1530-1536, 2005.)*

Glucose Lowering and Prevention of Heart Failure

Hyperglycemia is the hallmark of diabetes mellitus, and control of hyperglycemia is the primary treatment goal in managing patients with diabetes. Glycated hemoglobin, measured as HbA1c, reflects glycemic control over several months and is routinely used in monitoring treatment response clinically; it is a marker commonly used to evaluate treatment efficacy in research studies. Although reduction in HbA1c has been shown to reduce microvascular complications in diabetes, the usefulness of HbA1c as a surrogate marker for reduction in CV complications, including HF, remains questionable.[63–65] Furthermore, the impact of intensive glycemic control and glucose-lowering drugs on the prevention of HF largely remains unknown.

Impact of Glycemic Control (See also Chapter 13)

In general, there is consensus that clinicians should make every effort to control hyperglycemia, but evidence remains lacking regarding the effects (if any) of glucose control on the risk of HF.[66,67] Several studies have examined the impact of intensive glycemic control on vascular complications in diabetes, but, unfortunately, incident HF events were not uniformly collected nor independently adjudicated (see also **Chapter 26**). The best data regarding the role of intensive glycemic control in reducing the risk of HF come from a meta-analysis including the UKPDS,[68] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[69] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[70] and the Veterans Affairs Diabetes Trial (VADT).[71] Intensive glucose control was associated with a modestly lower risk of major CV events (HR 0.91, 95% CI 0.84-0.99), driven by a 15% reduction in risk of MI (HR 0.85, 95% CI 0.76-0.94). However, there was no difference for hospitalized or fatal HF events (HR 1.00, 95% CI 0.86-1.16).[72]

Antihyperglycemic Agents and Risk of Heart Failure

Thiazolidinediones

Thiazolidinediones (TZDs), namely rosiglitazone and pioglitazone, improve insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), which in turn reduces blood glucose levels.[73] Because of the efficacy in glycemic control, both as monotherapy and in combination with sulfonylureas, metformin, and insulin, the use of TZDs initially expanded rapidly worldwide after their clinical introduction in 1997. However, results from subsequent postmarketing observational studies, meta-analyses, and clinical trials raised the concern of increased risk for HF associated with TZD use.[73–79a]

The main side effects of TZDs indicating potential HF were signs of fluid retention such as pedal edema and weight gain. In the initial randomized trials, pedal edema was reported in 4.8% of patients receiving pioglitazone as monotherapy and in 6% to 7.5% when used in combinations with either metformin or sulfonylureas, compared with 1.2% to 2.5% in patients receiving either placebo or active comparators.[80] The incidence of edema is significantly higher in patients receiving concomitant insulin—15.3% of patients assigned to pioglitazone compared with 7.0% for insulin alone.[79] However, the incidence of investigator-reported edema was dramatically higher in the CV outcome trial of pioglitazone, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), which enrolled patients with long-duration diabetes and prevalent CV disease at trial entry. In this high-risk population, edema was observed in 27.4% of pioglitazone-treated patients compared with 15.9% of placebo-treated patients ($P<0.001$).[81,82] Similar trends were also observed with rosiglitazone, with edema observed in 4.8% of patients treated with rosiglitazone alone compared with 1.3% receiving placebo in randomized trials with rosiglitazone.[80] A higher incidence of edema has been observed with rosiglitazone use in combination with metformin or sulfonylurea (3% to 4%), compared with 1.1% to 2.2% in patients taking either comparator drug alone.[80] Similarly, concomitant use of insulin was associated with higher rates of edema, in 13.1% and 16.2% of patients taking rosiglitazone 4 or 8 mg/day, respectively, compared with 4.7% in those taking insulin alone.[83]

Pioglitazone and rosiglitazone also increase the risk of HF, as has been observed in patients with diabetes participating in major outcome trials designed to assess the CV safety of TZDs. In the PROactive trial, a significantly higher proportion of patients in the pioglitazone versus the placebo arm had an HF event (11% versus 8%; $P<0.0001$). Of these HF events, more pioglitazone than placebo patients (5.7% versus 4.1%) had serious HF—defined by requirement for hospitalization or prolongation of a hospital stay, HF that was fatal or life-threatening, or HF that resulted in persistent significant disability or incapacity ($P=0.007$). It is important to highlight that HF events were not prespecified endpoints in the PROactive study, but were detected as part of standard adverse event reporting and were later confirmed through adjudication of these safety events.[84] Similarly, rosiglitazone use increased the risk of HF hospitalization as observed in the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study.[79,79a] HF-related hospitalization or mortality occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2.10, 1.35-3.27; risk difference per 1000 person-years, 2.6, 1.1-4.1) (**Fig. 25-7**).[79a]

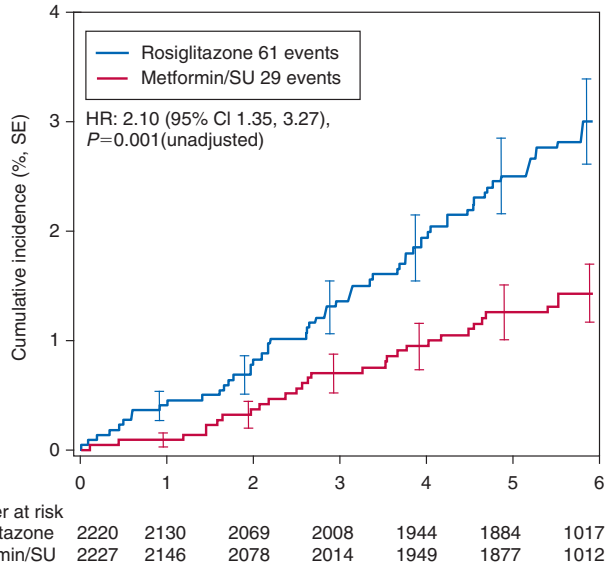


FIGURE 25-7 Kaplan-Meier plots of time to HF (fatal or nonfatal) in the RECORD study (intent-to-treat analysis). *(Modified from Komajda M, McMurray JJ, Beck-Nielsen H, et al: Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial,* Eur Heart J *31:824-831, 2010.)*

The mechanistic and causal relationship between TZDs and incident HF remains unclear. However, it is generally accepted that this is predominantly mediated by the effect of TZDs on increased fluid retention, hence unmasking underlying LV dysfunction (either diastolic or systolic), rather than direct cardiotoxicity. Nonetheless, clinicians should not discount the clinical significance of such events, because patients who developed HF events experienced high mortality rates (approximately 30%) during the follow-up period.

Earlier observations and findings from the PROactive and RECORD trials support the recommendations from the AHA and American Diabetes Association advising clinicians to assess the individual patient's risks before commencing TZDs (see **Box 25-1**) and to discontinue TZD use in patients with symptomatic HF.[79] More importantly, the experiences with TZDs highlighted the pitfall of relying on intermediate markers, such as HbA1c, in assessing the clinical effectiveness of glucose-lowering agents in the risk of macrovascular complications.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors (saxagliptin, sitagliptin, linagliptin, alogliptin, and vildagliptin) potentiate endogenous action of glucagon-like peptide 1 (GLP-1) by inhibiting its enzymatic degradation by DPP-4. Once-daily tablets with a low risk for hypoglycemia, DPP-4 inhibitors are increasingly used for glycemic control and have generally been considered safe with regard to CV risk based on the absence of adverse CV signals from phase I to IIIa trials.

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial enrolled over 16,000 patients with type 2 diabetes with or at increased risk for CV disease complications, evaluating randomized blinded treatment with saxagliptin versus placebo with a primary trial outcome of the composite of CV death, MI, and stroke. Overall, with a median 2.1-year trial follow-up, no benefit and no harm were detected for the primary major adverse CV event endpoint, meeting the regulatory threshold to exclude an upper 95% noninferiority confidence limit (HR 1.00; 95% CI 0.89-1.12). In the present context, a safety signal of increased risk for adjudicated HF hospitalization, a predefined component of the secondary efficacy endpoint, was observed with saxagliptin (3.5% versus 2.8%; HR 1.27, 95% CI 1.07-1.51; $P=0.007$).[85] This was an unexpected finding given prior observations of favorable myocardial effects of DPP-4 inhibitors in various HF experimental models[86–90]and, if these results from secondary trial analyses are true, raises the question of whether this may be a class effect. The Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care (EXAMINE) trial evaluated the effects of alogliptin versus placebo in 5380 patients with type 2 diabetes and a recent acute coronary syndrome event and, similar to SAVOR, demonstrated noninferiority with regard to the effect of alogliptin on the same three-point major adverse cardiovascular event (MACE) primary outcomes (HR 0.96; an upper boundary of the one-sided repeated confidence interval of 1.17)[90a] over a median follow-up of 18 months. In preliminary post hoc analyses (unpublished), a numeric increase in hospitalized HF events was observed in the alogliptin group, although this difference did not achieve statistical significance (3.9% versus 3.3%; HR 1.19, 95% CI 0.89-1.58). No mechanism has yet been proposed to account for the possibility of increased HF risk with DPP-4 inhibitors, and unfortunately no systematic assessment of cardiac structure or function was performed in either of these two clinical trials.

Insulin

The relationship between insulin use and risk of incident HF is unclear. Mechanistically, acute insulin administration is thought to be associated with fluid retention, potentially mediated by increased renal sodium retention caused by insulin,[91] and may theoretically contribute to overt HF among at-risk patients. Furthermore, chronic insulin administration is associated with weight gain and obesity, known risk factors for incident HF. However, data from prospective randomized trials are largely lacking, with the exception of one trial that assessed the CV effects of insulin glargine versus usual care in patients with early diabetes or prediabetic impaired glucose metabolism, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial. ORIGIN randomized individuals aged 50 years or older with CV risk factors, plus impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes, to receive insulin glargine or standard care. HF-related hospitalization was a prespecified component of the secondary composite endpoint. At median follow-up of 6.2 years (interquartile range, 5.8 to 6.7), there was no statistical difference in the risk of HF hospitalization between the study groups (HR 0.90; 95% CI 0.77-1.05; $P=0.16$).[92]

Evidence regarding the potential impact of other emerging glucose-lowering agents on risk for HF is mostly lacking, with numerous large CV outcome trials presently under way. GLP-1 agonists (exenatide, liraglutide) may have benefits for patients at risk for HF based on early studies demonstrating favorable effects on measures of cardiac function. For example, in a small study of patients with severe LV dysfunction after acute MI and reperfusion, patients treated with a 3-day GLP-1 infusion had a greater increase in LVEF (from 29% ± 2% to 39% ± 3%, $P<0.01$) compared with historical controls (28% ± 2% to 29% ± 2%).[93] GLP-1 treated patients also had a shorter length of hospital stay (6 versus 10 days, $P<0.02$). In another small randomized crossover clinical trial, patients with a low LVEF (<35%) and New York Heart Association (NYHA) Class III or IV HF symptoms, the GLP-1 agonist exenatide significantly increased cardiac index and decreased pulmonary capillary wedge pressure compared with placebo.[94]

Although there remains a lack of conclusive evidence on the long-term CVD outcomes with GLP-1 use, several studies have also shown favorable effects on CV risk factor profiles with these agents, such as lowering of systolic BP, weight loss, and possibly improvement in lipid profile, and these effects may in turn play a role in primary prevention of HF in patients with diabetes.[95]

Another class of agents that holds promise for potential benefits in preventing HF is the sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin). SGLT-2 antagonists inhibit glucose reclamation from the urine by blocking SGLT-2 in the proximal tubule, causing glucosuria to occur at much lower concentrations of plasma glucose. This results in loss of 200 to 400 kcal/day and some diuresis, thereby reducing body weight and lowering BP—both potentially favorable for HF prevention and suggesting a potential role for these drugs in the management of patients with type 2 diabetes and prevalent

HF. Until further data are available from ongoing clinical trial programs across this class of medications, all such effects on HF remain speculative.

CHALLENGES IN PREVENTION OF HEART FAILURE AND FUTURE DIRECTIONS

Preventing HF is a public health priority, and creating strategies to detect and treat patients at risk for HF will be critical. Recognition of major risk factors such as diabetes is important, but there is limited evidence to indicate the best strategies to identify patients to prevent them from progressing to stage B (asymptomatic with LV dysfunction) or to stage C or D (symptomatic HF). Moving forward, prevention strategies in the population with diabetes will likely require multidimensional efforts including the management of hyperglycemia and treatment of other common comorbidities associated with the risk of HF.[96,97] However, the evidence needed will likely require large, pragmatic clinical trials that rigorously evaluate different approaches to glucose-lowering strategies and/or other care for patients with diabetes.[98]

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26 Treatment of Heart Failure in Diabetes: Systolic Dysfunction, Diastolic Dysfunction, and Post-Acute Coronary Syndrome

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Diabetes and heart failure commonly occur together in a patient.[1] Up to a quarter of patients with diabetes also have heart failure, and approximately a third of patients with heart failure also have diabetes.[1] In this chapter we review the evidence-based medications device, and surgical treatment of heart failure. The primary focus is on patients with chronic heart failure, but when it exists, evidence about the treatment of patients with heart failure, left ventricular (LV) systolic dysfunction, or both after acute myocardial infarction is also reviewed. For each treatment we summarize the evidence base and, when possible, describe whether there is evidence specifically in patients with diabetes. As will become apparent, there is good evidence that the key pharmacologic and device therapies are as beneficial in patients with diabetes as in those without. Consequently, evidence-based guidelines on the treatment of heart failure apply to both those with and those without diabetes.[2]

TREATMENT OF HEART FAILURE IN PATIENTS WITH DIABETES MELLITUS

The landmark clinical trials providing the evidentiary basis for guidelines on the treatment of heart failure included a large proportion of patients with diabetes (**Table 26-1**). Consequently, we can make reasonable assumptions about the efficacy of most of the key treatments based on subgroup analyses. Unfortunately, the evidence base (**Table 26-2**) for patients with and without diabetes is confined to heart failure and reduced ejection fraction (HF-REF), and there is currently no proven treatment for heart failure and preserved ejection fraction (HF-PEF).[2]

Pharmacologic Therapy

Angiotensin-Converting Enzyme Inhibitors

Two key randomized controlled trials (RCTs), the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the treatment arm of the Studies of Left Ventricular Dysfunction (SOLVD-Treatment) assigned approximately 2800 patients with mild to severely symptomatic heart failure to placebo or enalapril.[3,4] Most patients were also treated with a diuretic and digoxin, but only approximately 10% of patients in each trial were treated with a beta blocker. In CONSENSUS, which enrolled patients with severely symptomatic heart failure, 53% of patients were treated with spironolactone.[3] Each trial showed that angiotensin-converting enzyme (ACE) inhibitor treatment reduced mortality (relative risk reduction [RRR] 27% in CONSENSUS and 16% in SOLVD-Treatment). In SOLVD-Treatment there was also an RRR of 26% in heart failure hospitalization.[4] The absolute risk reduction (ARR) in mortality in patients with mild to moderately symptomatic heart failure (SOLVD-Treatment) was 4.5%, equating to a number needed to treat (NNT) of 22 to postpone one death (over an average of 41 months).[2] The equivalent figures for severely symptomatic heart failure (CONSENSUS) were 14.6% for ARR and 7 for NNT (over an average of 6 months).[2] These findings are supported by a meta-analysis of smaller, short-term, placebo-controlled trials, which showed a clear reduction in mortality within only 3 months.[5] These trials also showed that ACE inhibitor treatment improves symptoms, quality of life, and functional capacity.

CONSENSUS had too few patients with diabetes (n = 253) to justify subgroup analysis. It is surprising to note that no diabetes subgroup analysis of SOLVD-Treatment has been published. However, the effectiveness of ACE inhibitors in patients with both diabetes and heart failure or postinfarction LV systolic dysfunction has been examined in a large meta-analysis of seven RCTs including SOLVD.[6] Of the 12,586 patients included in that analysis, 2398 had diabetes. For the endpoint of all-cause mortality, ACE inhibitors had a similar treatment benefit in patients with and without diabetes: hazard ratio (HR) 0.84 (95% CI 0.70-1.00) and 0.85 (95% CI 0.78-0.92), respectively.

Although detailed reports of adverse events in SOLVD have been published, these do not describe the subgroup of patients with diabetes.

The only large ACE inhibitor trial in HF-REF (n = 3164 patients) to provide detailed information on patients with diabetes (n = 611) was the Assessment of Treatment with

TABLE 26-1 Prevalence of Diabetes Mellitus in Key Trials in Patients with Heart Failure and Reduced Ejection Fraction

	NUMBER OF PATIENTS	PERCENT WITH DIABETES
CONSENSUS[3]	253	23
SOLVD-Treatment[4]	2569	26
CIBIS-2[29]	2647	12
MERIT-HF[31]	3991	24
COPERNICUS[30]	2289	26
SENIORS[32]	2128	26
Val-HeFT[15]	5010	25
CHARM-Alternative[14]	2028	27
CHARM-Added[18]	2548	30
RALES[40]	1663	25
EMPHASIS-HF[41]	2737	31
V-HeFT I	459	21
A-HeFT[46]	1050	41
DIG[52]	6800	28
GISSI-HF[48]	6975	28
SHIFT[47]	6558	31
COMPANION[57]	1520	41
CARE-HF[58]	813	26
MADIT-CRT[63]	1820	30
RAFT[60]	1798	34
SCD-HeFT[53]	1676	31
REMATCH	129	NR
STICH[64]	1212	40
HF-ACTION[66]	2331	32

Lisinopril and Survival (ATLAS) trial, which compared low-dose (2.5 to 5.0 mg daily) with high-dose (32.5 to 35.0 mg daily) lisinopril.[7,8] Overall, this trial showed no difference in the primary outcome of all-cause mortality over the median follow-up of 46 months but did show a significant reduction in a number of other endpoints including the composite of all-cause mortality or hospitalization for heart failure: HR 0.85 (0.78-0.93), $P<0.001$.[7] These findings, in addition to those of the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial, discussed later, suggest that higher doses of renin-angiotensin-aldosterone system (RAAS) blockers are better than lower doses.[9] In ATLAS, the greater relative benefit of high-dose lisinopril was similar in patients with and without diabetes, but because patients with diabetes were at greater risk, the absolute benefit of high-dose lisinopril was larger in patients with diabetes (**Figs. 26-1** and **26-2**). Overall, hypotension, renal dysfunction, and hyperkalemia were slightly more frequent in the high-dose group than in the low-dose group, but hypokalemia and cough were less common in the high-dose group.[8] The rate of study drug discontinuation was not greater in the high-dose group (17% versus 18% in the low-dose group). The occurrence of adverse effects with high-dose lisinopril was similar in those with and without diabetes with respect to hypotension and dizziness (35% versus 32%, respectively), renal dysfunction and hyperkalemia (29% versus 22%), and cough (12% versus 10%).[8]

Additional support for the use of ACE inhibitors comes from a trial in patients with a low ejection fraction (EF) but no symptoms of HF ("asymptomatic LV systolic dysfunction")—that is, the prevention arm of SOLVD (SOLVD-Prevention)—and three large (5966 patients in total) placebo-controlled, randomized, outcome trials in patients with heart failure, LV systolic dysfunction, or both after acute myocardial infarction.[10,11]

In the SOLVD-Prevention trial (which randomized 4228 patients with asymptomatic LV systolic dysfunction), there was a 20% RRR in death or heart failure hospitalization.[10] Although 15% of patients in SOLVD-Prevention had diabetes, outcomes in this subgroup were not reported.

In myocardial infarction trials that evaluated captopril (Survival and Ventricular Enlargement [SAVE]), ramipril (Acute Infarction Ramipril Efficacy [AIRE]), and trandolapril (Trandolapril Cardiac Evaluation [TRACE]), there was a 26% RRR in death and a 27% RRR in death or HF hospitalization.[11] The meta-analysis of these trials did not report a subgroup analysis according to baseline diabetes status.

In a subgroup analysis of SAVE, the RRR in all-cause mortality with captopril 50 mg three times daily in patients with diabetes was 12% (-21% to 36%) compared with 20% (2% to 35%) in those without.[12] For the composite outcome of cardiovascular (CV) mortality, heart failure requiring either ACE inhibitor treatment or hospitalization, or the occurrence of recurrent infarction, these reductions were 17% (-6% to 36%) and 26% (12% to 37%), respectively. In a later report describing a multivariable analysis, captopril was reported to decrease all-cause mortality (HR 0.81; 95% confidence interval [CI] 0.68-0.96) as well as CV mortality or morbidity (HR 0.75; 95% CI 0.65-0.86). The benefit of captopril was similar among patients with (HR 0.83; 95% CI 0.63-0.87) and without (HR 0.80; 95% CI 0.64-0.94) diabetes (interaction $P=0.45$).[13]

Angiotensin Receptor Blockers

More patients were randomized into large angiotensin receptor blocker (ARB) outcome trials than ACE inhibitor trials.

An ARB was examined as an alternative to an ACE inhibitor in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Alternative), which was a placebo-controlled RCT with candesartan in 2028 patients with a left ventricular ejection fraction (LVEF) of 40% or lower who were intolerant of an ACE inhibitor.[14] Treatment with candesartan resulted in an RRR of CV or heart failure hospitalization of 23% (ARR 7%, NNT 14, over 34 months of follow-up). Valsartan was also beneficial in the subset of 366 patients in the Valsartan Heart Failure Trial (Val-HeFT) not treated with an ACE inhibitor.[15] Another trial, the Evaluation of Losartan in the Elderly (ELITE II), failed to show that losartan 50 mg daily was as effective as captopril 50 mg three times daily.[16] However, a subsequent RCT, the HEAAL trial,[9] showed that 150 mg daily of losartan (n = 1927) was superior to 50 mg daily (n = 1919), supporting the similar findings of the ATLAS trial with the ACE inhibitor lisinopril (see earlier).[7] In HEAAL, there was a RRR of 10% in death or HF hospitalization in the high-dose losartan group ($P=0.027$) over a median follow-up of 4.7 years.[9]

The efficacy and safety of adding an ARB to an ACE inhibitor has been studied. Two key placebo-controlled RCTs, Val-HeFT[17] and CHARM-Added,[18] randomized approximately 7600 patients with mild to severely symptomatic heart failure to placebo or an ARB (valsartan and candesartan), added to an ACE inhibitor (in 93% of patients in Val-HeFT and all patients

TABLE 26-2 Key Randomized Controlled Trials[a] in Symptomatic Heart Failure with Reduced Ejection Fraction

TREATMENT, TRIAL, AND YEAR PUBLISHED	N	SEVERITY OF HEART FAILURE SYMPTOMS	BACKGROUND TREATMENT[b]	TREATMENT ADDED	TRIAL DURATION (YEARS)	PRIMARY ENDPOINT	RELATIVE RISK REDUCTION (%)	EVENTS PREVENTED PER 1000 PATIENTS TREATED		
								Death	HF Hospitalization	Death or HF Hospitalization
ACE Inhibitors										
CONSENSUS, 1987	253	End stage	Spiro	Enalapril 20 mg bid	0.54[e]	Death	40	146	—	
SOLVD-T, 1991	2569	Mild to severe	—	Enalapril 20 mg bid	3.5	Death	16	45	96	108
BBs										
CIBIS-2, 1999	2647	Moderate to severe	ACE inhibitor	Bisoprolol 10 mg qd	1.3[e]	Death	34	55	56	—
MERIT-HF, 1999	3991	Mild to severe	ACE inhibitor	Metoprolol CR/XL 200 mg qd	1.0[e]	Death	34	36	46	63
COPERNICUS, 2001	2289	Severe	ACE inhibitor	Carvedilol 25 mg bid	0.87[e]	Death	35	55	65	81
SENIORS, 2005	2128	Mild to severe	ACE inhibitor +spiro	Nebivolol 10 mg qd	1.75	Death or CV hospitalization	14	23	0	—
ARBs										
Val-HeFT, 2001	5010	Mild to severe	ACE inhibitor	Valsartan 160 mg bid	1.9	CV death or morbidity	13	0	35	33[f]
CHARM-Alternative, 2003	2028	Mild to severe	BB	Candesartan 32 mg qd	2.8	CV death or HF hospitalization	23	30	31	60
CHARM-Added, 2003	2548	Moderate to severe	ACE inhibitor+BB	Candesartan 32 mg qd	3.4	CV death or HF hospitalization	15	28	47	39
MRAs										
RALES, 1999	1663	Moderate to severe	ACE inhibitor	Spiro 25-50 mg qd	2.0[e]	Death	30	113	95	—
EMPHASIS-HF, 2011	2737	Mild	ACE inhibitor+BB	Eplerenone 25-50 mg qd	1.75[e]	CV death or HF hospitalization	37	30	64	66
H-ISDN										
V-HeFT-1, 1986	459	Mild to severe	—	Hydralazine 75 mg tid-qid ISDN 40 mg qid	2.3	Death	34	52	0	—
A-HeFT, 2004	1050	Moderate to severe	ACE inhibitor–BB +spiro	Hydralazine 75 mg tid ISDN 40 mg tid	0.83[e]	Composite	—	40	80	—
Digitalis Glycoside										
DIG, 1997	6800	Mild to severe	ACE inhibitor	Digoxin	3.1	Death	0	0	79	73
n-3 PUFA										
GISSI-HF, 2008	6975	Mild to severe	ACE inhibitor–BB–spiro	n-3 PUFA 1 g qd	3.9	Death Death or CV hospitalization	8	—	—	—
CRT										
COMPANION, 2004	925	Moderate to severe	ACE inhibitor+BB +spiro	CRT	1.35[e]	Death or any hospitalization	19	38	—	87
CARE-HF, 2005	813	Moderate to severe	ACE inhibitor+BB +spiro	CRT	2.45	Death or CV hospitalization	37	97	151	184

Continued

TABLE 26-2 Key Randomized Controlled Trials[a] in Symptomatic Heart Failure with Reduced Ejection Fraction—cont'd

TREATMENT, TRIAL, AND YEAR PUBLISHED	N	SEVERITY OF HEART FAILURE SYMPTOMS	BACKGROUND TREATMENT[b]	TREATMENT ADDED	TRIAL DURATION (YEARS)	PRIMARY ENDPOINT	RELATIVE RISK REDUCTION (%)	EVENTS PREVENTED PER 1000 PATIENTS TREATED[c,d]		
								Death	HF Hospitalization	Death or HF Hospitalization
CRT-D										
COMPANION, 2004	903	Moderate to severe	ACE inhibitor+BB +spiro	CRT-ICD	1.35[e]	Death or any hospitalization	20	74	—	114
MADIT-CRT, 2009	1820	Mild	ACE inhibitor+BB +spiro+ICD	CRT-ICD	2.4[e]	Death or HF event[g]	34	5	—	—
RAFT, 2011	1798	Mild to moderate	ACE inhibitor–BB +spiro+ICD	CRT-ICD	3.23	Death or HF hospitalization	25	53	66	70
ICD										
SCD-HeFT, 2005	1676	Mild to severe	ACE inhibitor+BB	ICD	3.8	Death	23	—	—	—
VAD										
REMATCH, 2001	129	End stage	ACE inhibitor +spiro	LVAD	1.8	Death	48	282	—	—
CABG										
STICH, 2011	1212	Mild to severe	ACE inhibitor+BB +spiro	CABG	4.67	Death	14	48	—	63
Exercise Training										
HF-ACTION, 2009	2331	Mild to severe	ACE inhibitor+BB +spiro	Exercise training	2.5	Death or any hospitalization	7	6	—	—

HF hospitalization = patients with at least one hospital admission for worsening HF; some patients had multiple admissions.

ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta blocker; CABG = coronary artery bypass grafting; CR/XL = controlled release/extended release; CRT = cardiac resynchronization therapy (biventricular pacing); CRT-D = CRT device that also defibrillates; CV = cardiovascular; HF = heart failure; H-ISDN = combination of hydralazine and isosorbide dinitrate; ICD = implantable cardioverter defibrillator; ISDN = isosorbide dinitrate; LVAD = left ventricular assist device; n-3 PUFA = omega-3 polyunsaturated fatty acid; MRA = mineralocorticoid receptor antagonist; spiro = spironolactone; VAD = ventricular assist device.

[a] Excluding active controlled trials.

[b] In more than one third of patients: ACE inhibitor + BB means ACE inhibitors used in almost all patients and BB in the majority. Most patients also taking diuretics, and many digoxin (except in DIG). Spironolactone was used at baseline in 5% Val-HeFT, 8% MERIT-HF, 17% CHARM-Added, 19% SCD-HeFT, 20% COPERNICUS, and 24% CHARM-Alternative.

[c] Relative risk reduction in primary endpoint.

[d] Individual trials may not have been designed or powered to evaluate effect of treatment on these outcomes.

[e] Stopped early for benefit.

[f] Primary endpoint also included treatment of HF with intravenous medications for 4 hours or more without admission and resuscitated cardiac arrest (both added small numbers).

[g] Heart failure hospitalization or heart failure treated with intravenous therapy as an out patient.

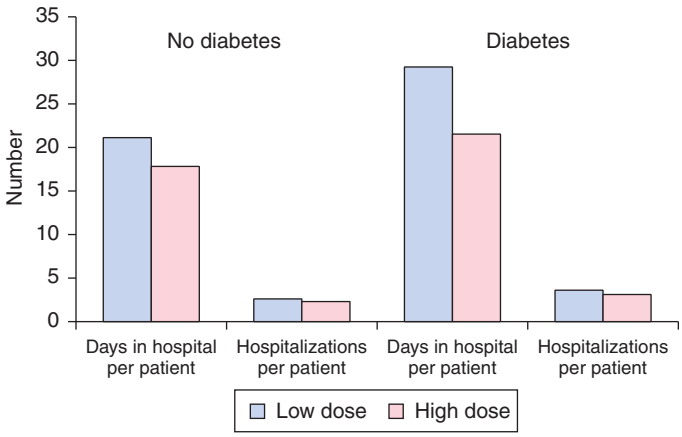


FIGURE 26-1 **Effect of high-dose compared with low-dose lisinopril in patients with HF-REF in the ATLAS trial.**

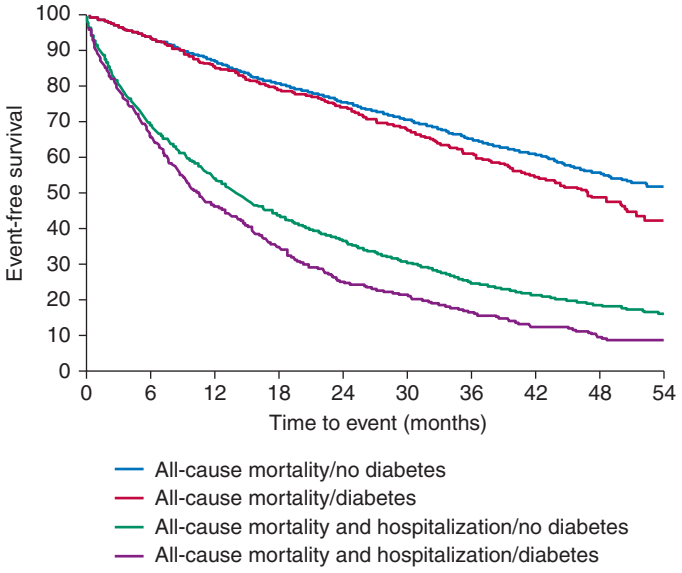


FIGURE 26-2 **Effect of high-dose compared with low-dose lisinopril in patients with HF-REF in the ATLAS trial: all-cause mortality and all-cause mortality or hospitalization.** Comparison of patients with and without diabetes.

in CHARM-Added). In addition, approximately a third of patients in Val-HeFT and just over half in CHARM-Added were treated with a beta blocker, but few patients were taking a mineralocorticoid receptor antagonist (MRA). Each of these two trials showed that ARB treatment reduced the risk of heart failure hospitalization (RRR 24% in Val-HeFT and 17% in CHARM-Added). There was a 16% RRR in the risk of CV death with candesartan in CHARM-Added, but CV death was not reduced by valsartan in Val-HeFT.[17,18] The ARR in the primary composite mortality-morbidity endpoint in patients with mild to moderately severe symptoms was 4.4%, equating to an NNT (for an average of 41 months to postpone one event) of 23 in CHARM-Added. The equivalent figures for Val-HeFT were ARR 3.3% and NNT 30 (over an average of 23 months). The CHARM trials and Val-HeFT also showed that ARBs improve symptoms and quality of life. Other trials showed that these agents improve exercise capacity.

Pooling the two CHARM HF-REF trials (CHARM-Alternative and CHARM-Added)[19] showed that treatment with candesartan reduced the risk of CV death or heart failure hospitalization with an HR of 0.82 (95% CI 0.74-0.90,

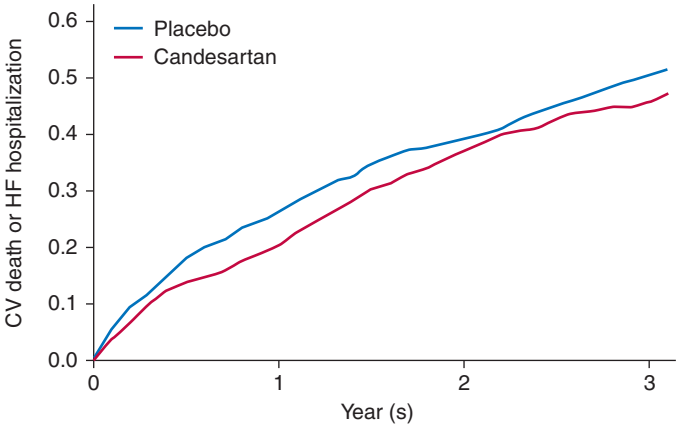


FIGURE 26-3 **Effect of candesartan compared with placebo in patients with HF-REF and diabetes in the CHARM program: CV mortality or heart failure hospitalization.**

$P<0.001$) and all-cause mortality (HR 0.84; 95% CI 0.79-0.98; $P=0.018$).[19] The effect of treatment was not statistically different in patients with and without diabetes (interaction $P=0.12$). The effect of candesartan in patients with HF-REF and diabetes in the CHARM program is shown in **Figure 26-3**. In Val-HeFT the effect of valsartan was not statistically different in the subgroup of patients with diabetes (interaction P value not provided).

In HEAAL the treatment effect of high-dose compared with low-dose losartan was not different in the subgroup of patients with diabetes (HR 0.96; 95% CI 0.82-1.12; $P=0.35$). However, in all three reports, the point estimate for the HR was less favorable in patients with diabetes than in those without.

There is little information about the tolerability of ARBs in diabetes. In the overall CHARM program, patients with diabetes had double the risk of developing hyperkalemia on candesartan compared with those without diabetes.[20]

Additional support for the use of ARBs comes from the Valsartan in Acute Myocardial Infarction (VALIANT) trial, a trial in which 14,703 patients with heart failure, LV systolic dysfunction, or both after acute myocardial infarction were assigned to treatment with captopril 50 mg three times daily, valsartan 160 mg twice daily, or the combination.[21] Valsartan was found to be noninferior to captopril overall, but combination therapy was not better than monotherapy. The effect of valsartan relative to captopril was not significantly different in patients with and without diabetes, either for all-cause mortality (interaction $P=0.10$) or CV mortality and morbidity (interaction $P=0.12$).

In the Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial,[22] losartan 50 mg once daily did not demonstrate noninferiority when compared with captopril 50 mg three times daily, which, considered in conjunction with the findings of ELITE II and HEAAL, suggests that 50 mg of losartan daily is a suboptimal dose.

Direct Renin Inhibitors

Recently, a third approach to blocking the renin-angiotensin system has been tested in heart failure. In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) trial, patients with an LVEF of 40% or lower, elevated natriuretic peptides, and signs and symptoms of fluid overload who had been admitted on an emergency basis to a hospital for the treatment of heart failure were randomized, when stabilized (a median 5 days after admission), to 12 months of

treatment with the direct renin inhibitor (DRI) aliskiren 150 mg daily (increased to 300 mg as tolerated) or placebo daily. The study drug was given in addition to standard therapy, which included diuretics (96%), beta blockers (83%), ACE inhibitors or ARBs (84%), and MRAs (57%). The main endpoint was the composite of CV death or heart failure rehospitalization at 6 months (the main secondary endpoint was this composite at 12 months). In total, 1639 patients were randomized and 1615 patients included in the final efficacy analysis cohort (808 aliskiren, 807 placebo). The mean age was 65 years, LVEF was 28%, and estimated glomerular filtration rate (eGFR) was 67 mL/min/1.73 m^2; 41% of patients had diabetes mellitus. Overall, 24.9% of patients receiving aliskiren (77 CV deaths, 153 HF rehospitalizations) and 26.5% of patients receiving placebo (85 CV deaths, 166 HF rehospitalizations) experienced the primary endpoint at 6 months (HR 0.92, 95% CI 0.76-1.12; $P=0.41$). At 12 months, the rates were 35.0% for aliskiren (126 CV deaths, 212 HF rehospitalizations) and 37.3% in the placebo group (137 CV deaths, 224 HF rehospitalizations); HR 0.93, 95% CI 0.79-1.09; $P=0.36$. The rates of hypotension, renal dysfunction, and hyperkalemia were higher in the aliskiren group compared with placebo.

Although there was no evidence for heterogeneity of treatment effect for any subgroup with respect to the primary endpoint, there was a significant interaction between treatment and diabetes status at baseline (patients with diabetes: HR 1.16, 95% CI 0.91-1.47; no diabetes group: HR 0.80, 95% CI 0.64-0.99; $P=0.03$ for interaction). There was also an interaction for all-cause mortality at 1 year—diabetes patients: HR 1.64, 95% CI 1.15-2.33; no diabetes group: HR 0.69, 95% CI 0.50-0.94; $P=0.001$ for interaction). Among patients with a history of diabetes, 24.1% of patients died in the aliskiren group compared with 17.4% of patients in the placebo group, whereas the rates of death in patients without diabetes were 15.3% and 20.0% in the two treatment groups, respectively.

Whereas subgroup findings may arise by chance and are normally only considered hypothesis generating, similar findings of increased risks of hypotension, renal dysfunction, and hyperkalemia in the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) convinced regulatory agencies to declare that aliskiren is contraindicated in patients with diabetes who are receiving an ARB or ACE inhibitor and in patients with an eGFR below 60 mL/min/1.73 m^2. In Europe this prohibition was extended to monotherapy with aliskiren in patients with diabetes or chronic kidney disease, which resulted in patients with diabetes having study drug discontinued in the ongoing Aliskiren Trial of Minimizing Outcomes for Patients with Heart Failure (ATMOSPHERE) comparing aliskiren (up to 300 mg once daily), enalapril (10 mg twice daily), and the combination of aliskiren and enalapril in over 7000 patients with chronic HF-REF. Despite this, ATMOSPHERE is expected to remain adequately powered and to run to its planned completion.[23–27]

Beta Blockers

There is more evidence showing the benefit of a beta blocker in HF-REF than any other pharmacologic therapy, yet patients with diabetes are less likely to receive this type of treatment than those without diabetes.[28]

Three key trials—the Cardiac Insufficiency Bisoprolol Study II (CIBIS II),[29] Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS),[30] and Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)[31]— randomized almost 9000 patients with mild to severely symptomatic heart failure to placebo or a beta blocker (bisoprolol, carvedilol, or metoprolol succinate CR/XL). More than 90% of the patients were on background treatment with an ACE inhibitor or an ARB. Each of these three trials showed that beta blocker treatment reduced mortality (RRR approximately 34% in each trial) and heart failure hospitalization (RRR 28% to 36%) within approximately a year of starting treatment. The ARR in mortality (after 1 year of treatment) in patients with mild to moderate symptoms (CIBIS II and MERIT-HF combined) was 4.3%, equating to an NNT for 1 year to postpone one death of 23. The equivalent figures for severely symptomatic patients (COPERNICUS) were ARR 7.1% and NNT 14. These findings are supported by another placebo-controlled trial, the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)[32] in 2128 elderly (70 years or older) patients, 36% of whom had an EF below 35%. Treatment with nebivolol resulted in an RRR of 14% in the primary composite endpoint of death or CV hospitalization but did not reduce mortality. The findings of these trials are also supported by an earlier program of studies with carvedilol (U.S. carvedilol studies).

Several subgroup analyses from these trials and meta-analyses have shown the efficacy and safety of beta blockers specifically in patients with HF-REF and diabetes. In a meta-analysis of six trials, Haas and colleagues[33] found that beta blocker therapy reduced all-cause mortality in patients with diabetes (n=3230; HR 0.84, 95% CI 0.73-0.96) and those without diabetes (n=9899; HR 0.72, 95% CI 0.65-0.79). Shekelle, and colleagues[6] analyzed data from three trials (CIBIS-II, MERIT-HF, and COPERNICUS) that gave a relative risk of 0.77 (95% CI 0.61, 0.96) in patients with diabetes (n=1883) and 0.65 (95% CI 0.57, 0.74) in patients without diabetes (n=7042). A third meta-analysis focused on seven trials in which carvedilol was used,[34] including a postinfarction trial, which collectively enrolled 1411 patients with diabetes (24.5% of total patients). In all randomized patients, carvedilol reduced all-cause mortality (RRR 34%, 95% CI 23%-44%; $P<0.0001$). In patients with diabetes the RRR was 28% (95% CI 3% to 46%; $P=0.029$), and it was 37% (95% CI 22% to 48%; $P<0.0001$) in patients without diabetes (interaction $P=0.25$). The NNT for 1 year to prevent one death was 23 (95% CI 17-36) for all patients, 25 (14-118) in patients with diabetes and 23 (95% CI 17-37) in those without diabetes.

The MERIT-HF investigators published a detailed analysis of both the efficacy and the safety of metoprolol succinate compared with placebo in patients with (n=985) and without (n=3006) diabetes.[35] It is important to note that this analysis also reports key nonfatal outcomes (and fatal or nonfatal composites) and shows that these too were reduced by beta blocker therapy in patients with diabetes (**Figs. 26-4** and **26-5**). Patients with diabetes were more likely to experience adverse events (in either treatment group) compared with patients without diabetes. However, patients receiving metoprolol succinate were less likely to experience adverse events than those treated with placebo, both patients with and those without diabetes, and were less likely to discontinue the study drug. The average dose of metoprolol succinate taken during the trial was similar in patients with (162 mg at the last follow-up visit) and without (156 mg) diabetes. There was no difference between metoprolol succinate and placebo in relation to adverse events indicating impaired glycemic control.

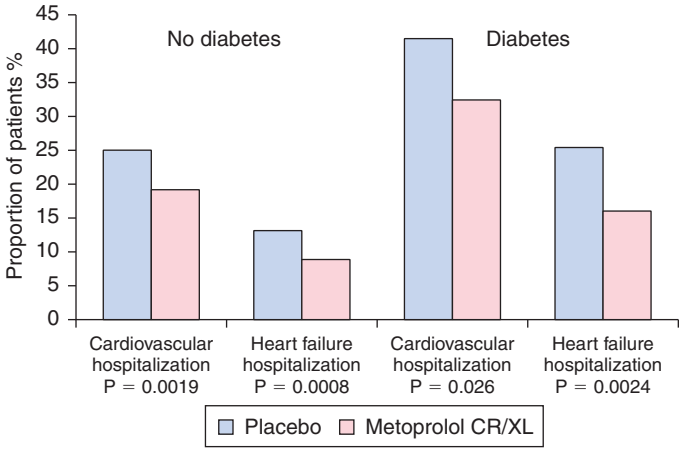


FIGURE 26-4 Effect of metoprolol succinate in patients with HF-REF in the MERIT-HF trial.

Hypoglycemia is a particular concern in patients with diabetes treated with insulin or sulfonylureas. Theoretically, beta blockers could alter awareness of hypoglycemia by decreasing palpitations and tremor and could prolong recovery from hypoglycemia by blocking beta$_2$ receptors, which partly control glucose production in the liver.

However, among patients with diabetes in MERIT-HF, only three (0.6%) in the placebo group and four (0.8%) in the metoprolol succinate group had an adverse event related to hypoglycemia (in each case in patients taking insulin).

Another trial, the Carvedilol or Metoprolol European Trial (COMET),[36,37] showed that carvedilol reduced mortality compared with short-acting metoprolol tartrate (different from the long-acting succinate formulation used in MERIT-HF). In COMET, both patients with and those without diabetes had similar risk reductions for mortality on carvedilol compared with metoprolol: relative risk 0.85, 95% CI 0.69-1.06, $P=0.147$ for those with diabetes; and RR 0.82, 95% CI 0.71-0.94, $P=0.006$ for patients without diabetes (interaction $P=0.77$).

Of note, in a trial in patients with hypertension and diabetes, carvedilol had a favorable effect on glycated hemoglobin (and insulin sensitivity) compared with metoprolol tartrate.[38]

The benefit of beta blockers in heart failure is supported by a placebo-controlled trial in 1959 patients with an LVEF of 40% or lower after acute myocardial infarction—the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial,[39] in which the RRR in mortality with carvedilol was 23% during a mean follow-up of 1.3 years. Among the 437 patients with diabetes in CAPRICORN, the placebo-carvedilol HR for all-cause mortality was 0.93 (95% CI 0.61-1.44) compared with HR 0.71 (95% CI 0.53-0.96) in those without diabetes (n = 1522). The corresponding figures for the composite of death or CV hospitalization were HR 0.88 (95% CI 0.80-1.13) and HR 0.95 (95% CI 0.66-1.16), respectively.

In summary, beta blockers in patients with diabetes and heart failure lead to significant improvements in morbidity and mortality associated with heart failure, benefits that far outweigh the theoretical risks related to hypoglycemia and minor changes in glycated hemoglobin and lipids.

Mineralocorticoid Receptor Antagonists

In the Randomized Aldactone Evaluation Study (RALES),[40] 1663 patients with an EF of 35% or lower and in New York Heart Association (NYHA) functional class III (if in class IV within the past 6 months) or IV were randomized to placebo or spironolactone 25 to 50 mg once daily, added to conventional treatment. When this trial was conducted, beta blockers were not widely used to treat heart failure, and only 11% of patients were treated with a beta blocker. Treatment with spironolactone led to an RRR in all-cause mortality of 30% and an RRR in heart failure hospitalization of 35%. The ARR in mortality (after a mean of 2 years of treatment) was 11.4%, equating to an NNT (for 2 years to postpone one death) of 9. More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial[41] enrolled 2737 patients aged 55 years or older with NYHA functional class II symptoms and an EF of 30% or lower (≤35% if the QRS duration was >130 milliseconds). Patients had to have either a CV hospitalization within the previous 6 months or an elevated plasma natriuretic peptide concentration and to have been treated with an ACE inhibitor, ARB, or both, and a beta blocker. Treatment with eplerenone (up to 50 mg once daily) for an average of 21 months led to a RRR of 37% in CV death or heart failure hospitalization. There were also reductions in the risk of death from any cause (24%), CV death (24%), all-cause hospitalization (23%), and heart failure hospitalization (42%). The ARR in the primary composite mortality-morbidity endpoint was 7.7%, equating to an NNT (for an average of 21 months to postpone one event) of 13. The ARR in all-cause mortality was 3%, equating to an NNT of 33.

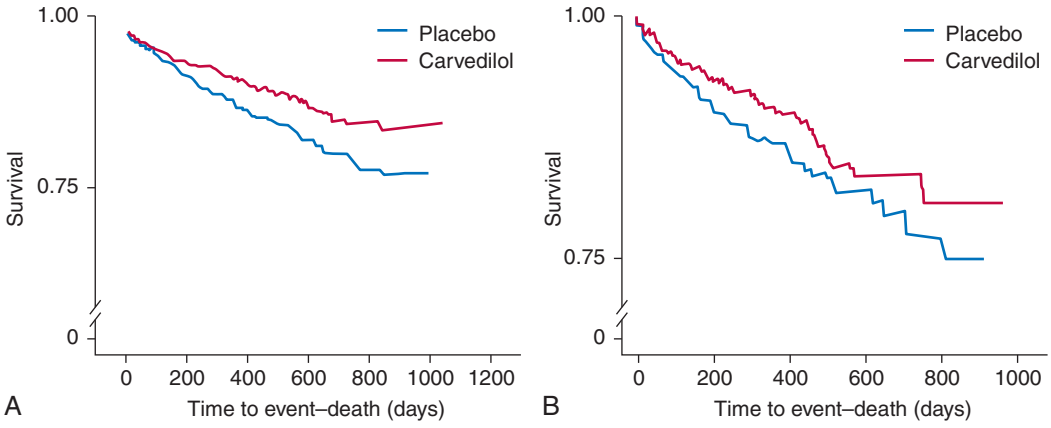


FIGURE 26-5 Effect of carvedilol on all-cause mortality in heart failure patients without (A) and with (B) diabetes.

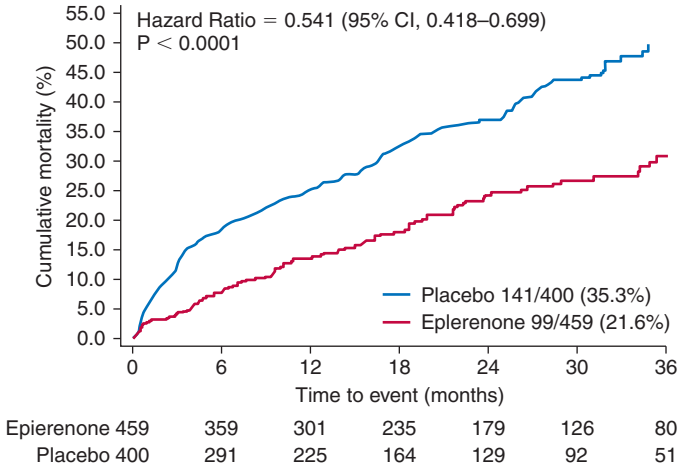


FIGURE 26-6 Effect of eplerenone on all-cause mortality in patients with HF-REF and diabetes in EMPHASIS-HF.

In RALES, the mortality benefit was similar in patients with and without diabetes, with HR of 0.70 (95% CI 0.52-0.94) and HR 0.70 (95% CI 0.60-0.82), respectively.[42] In EMPHASIS-HF, the treatment benefit was consistent in patients with and without diabetes (interaction $P=0.10$; **Fig. 26-6**).

The finding that MRAs are beneficial in patients with chronic HF-REF is supported by another trial, the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[43] which enrolled 6632 patients with an EF of 40% or lower and HF or diabetes 3 to 14 days after acute myocardial infarction. Patients were randomized to placebo or eplerenone 25 to 50 mg once daily added to conventional treatment including an ACE inhibitor or ARB and a beta blocker. Treatment with eplerenone reduced all-cause mortality (RR 0.85, 95% CI 0.75-0.96; $P=0.008$), and reduced the rate of the other co-primary endpoint, a composite of death from CV causes or hospitalization for CV events (RR 0.87, 95% CI 0.79-0.95; $P=0.002$).[31]

A subgroup analysis for the 1483 patients with diabetes in EPHESUS has been published.[44] The eplerenone-placebo relative risk of death from any cause in these patients was RR 0.85 (95% CI 0.68-1.05). The relative risk of death from CV causes or hospitalization for CV events was RR 0.83 (95% CI 0.71-0.98).

Hyperkalemia has been a particular concern with MRAs, and it has been suggested that this risk may be greater in patients with diabetes. There was an increase in the incidence of a potassium concentration exceeding 5.5 mmol/L with eplerenone in patients with diabetes—63 (14.1%) compared with 33 (8.5%) on placebo, $P=0.01$. However, the proportion with a serum potassium level above 6.0 mmol/L was not statistically different between the groups (17 [3.8%] compared with 8 [2.1%] on placebo, $P=0.16$), and there was no increase in the rate of discontinuation of eplerenone for hyperkalemia in those with diabetes compared with those without (interaction $P=0.12$). Similar findings we reported in EPHESUS. Among patients with diabetes in EPHESUS, hypoglycemia was reported as an adverse event in 11 patients (1.5%) treated with eplerenone and 11 patients (2.6%) treated with placebo ($P=0.14$).[44]

Some investigators believe that eplerenone may have more favorable metabolic effects than spironolactone in patients with diabetes.[45]

Nitrates and Hydralazine

The African-American Heart Failure Trial (A-HeFT)[46] examined the safety and efficacy of fixed-dose combination therapy with isosorbide dinitrate and hydralazine hydrochloride, added to an ACE inhibitor or ARB, beta blocker, and MRA in African Americans with NYHA class III or IV heart failure.[46] The trial had an unusual composite outcome including survival, hospitalization, and quality of life but was stopped early because treatment with this medication combination led to a 43% reduction in all-cause death (HR 0.57, 95% CI 0.37-0.89; $P=0.01$). There was also a 33% reduction in first hospitalization for heart failure ($P=0.001$). A very large proportion (41%) of patients in the study had diabetes. The treatment effect on mortality was similar in patients with (HR 0.56 [95% CI 0.28-1.15]) and without (HR 0.59 [95% CI 0.34-1.03]) diabetes.

Ivabradine

The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT)[47] enrolled 6588 patients in NYHA functional class II to IV, sinus rhythm with a rate of 70 beats/min or greater, and an EF of 35% or lower. Patients were also required to have had an HF hospitalization in the previous 12 months. They were randomized to ivabradine (uptitrated to a maximal dosage of 7.5 mg twice daily) or placebo, added to a diuretic and an ACE inhibitor or ARB, a beta blocker, and an MRA. Only 26% of patients were, however, on full-dose beta blocker. The median follow-up was 23 months. The RRR in the primary composite outcome of CV death or HF hospitalization was 18% (HR 0.82, 95% CI 0.75-0.90; $P<0.0001$); the reduction in CV death (or all-cause death) was not significant, but the RRR in HF hospitalization was 26%. Ivabradine also improved LV function and quality of life. In the 1979 patients with diabetes, the HR for the primary composite endpoint was 0.81 (95% CI 0.69-0.95), and in those without diabetes (n = 4526) it was 0.83 (95% CI 0.74-0.93).

Omega-3 Polyunsaturated Fatty Acids

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure (GISSI-HF)[48] trial examined the effect of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in 6975 patients with NYHA class II to IV symptoms and an EF of 40% or lower (or if not ≤40%, HF hospitalization in the previous year). Patients were randomized to placebo or 1 g daily of an n-3 PUFA preparation added to background treatment with an ACE inhibitor or ARB beta blocker and an MRA. The median follow-up was 3.9 years; n-3 PUFA treatment led to an hazard reduction of 8% (HR 0.92, 95% CI 0.85-1.00) in the co-primary composite outcome of death or CV hospitalization in an adjusted analysis (adjusted $P=0.009$). There was no reduction in heart failure hospitalization, but there was a 9% RRR in all-cause mortality, the other co-primary endpoint (adjusted $P=0.041$), a 10% RRR in CV mortality (adjusted $P=0.045$), and 7% RRR in CV hospitalization (adjusted $P=0.026$). In patients with diabetes, the HR for the composite outcome of death or CV hospitalization was 0.89 (95% CI 0.80-0.99), and in those without diabetes it was 0.96 (95% CI 0.89-1.04).

The findings in GISSI-HF are supported by one post–myocardial infarction RCT (GISSI-Prevenzione)[49,50] but not by another (OMEGA),[51] although neither of these trials was specifically conducted with patients with LV systolic dysfunction or heart failure. In GISSI-Prevenzione, 11,324



patients enrolled after a recent (within 3 months) myocardial infarction received placebo or 1 g daily of n-3 PUFA. n-3 PUFA reduced the risk of the primary composite outcome of death, myocardial infarction, or stroke by 10% (95% CI 1-18%) by two-way analysis, and by 15% (95% CI 2-26%) by four-way analysis. This benefit was attributable to a decrease in the risk of all-cause mortality (14% [95% CI 3-24%] by two-way analysis, 20% [95% CI 6-33%] by four-way analysis) and CV mortality (17% [95% CI 3-29%] by two-way analysis, 30% [95% CI 13-44%] by four-way analysis). In a follow-up paper, the GISSI-Prevenzione[49,50] investigators reported that the adjusted RR for all-cause mortality in patients with diabetes was 0.72 (95% CI 0.52-0.99) and in those without diabetes RR was 0.82 (95% CI 0.67-1.01), interaction $P=0.50$.

OMEGA randomized 3851 patients 3 to 14 days after acute myocardial infarction to placebo or 1 g n-3 PUFA daily for 1 year.[51] Outcomes did not differ between treatment groups.

Digoxin

A single large morbidity-mortality trial, the Digitalis Investigation Group (DIG) trial,[52] was conducted in 6800 patients with an EF of 45% or lower and in NYHA functional class II to IV. Patients were randomized to placebo or digoxin (mostly 0.25 mg once daily), added to a diuretic and an ACE inhibitor (DIG was performed before beta blockers were widely used for heart failure), and treated for an average of 3 years. Digoxin did not reduce all-cause mortality, the primary endpoint, but did lead to a RRR of 28% (RR 0.72, 95% CI 0.66-0.79; $P<0.001$) in heart failure hospitalization. The ARR was 7.9%, equating to an NNT (for 3 years to postpone one patient admission) of 13. We are not aware of any specific data from randomized trials of digitalis glycosides reporting the effect of treatment separately in patients with diabetes.

Diuretics

Diuretics are usually required to treat the symptoms and signs of fluid overload in patients with heart failure. There are no clinical trials examining their efficacy specifically in patients with both diabetes and heart failure. Theoretically thiazide diuretics can lead to increased insulin resistance and subsequent worsening of glycemic control.

Devices and Surgery

Implantable Cardioverter Defibrillators

Approximately half of the deaths in patients with HF-REF, especially in those with milder symptoms, occur suddenly and are usually caused by a ventricular arrhythmia. Prevention of sudden death is therefore an important goal in HF. Although the key neurohumoral antagonists mentioned earlier reduce the risk of sudden death, they do not abolish it. Antiarrhythmic medications do not decrease this risk at all (and may even increase it). Consequently, implantable cardioverter defibrillator (ICDs) have an important role to play in reducing the risk of death from ventricular arrhythmias either alone or combined with cardiac resynchronization therapy (CRT). An ICD should be considered in any patient with an unprovoked, sustained, symptomatic ventricular arrhythmia.[2] ICDs also have a role in the primary prevention of arrhythmic death. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[53] enrolled 2521 patients with nonischemic dilated cardiomyopathy or ischemic heart failure, no prior symptomatic ventricular arrhythmia, and an EF of 35% or lower who were in NYHA functional class II or III. These patients were randomized to placebo, amiodarone, or an ICD, in addition to receiving conventional treatment including an ACE or ARB and a beta blocker; MRA use was not reported. ICD treatment led to an RRR in death of 23% (RR 0.77, 95% CI 0.62-0.96; $P=0.007$) over a median follow-up of 45.5 months. Amiodarone did not reduce mortality. The ARR in mortality with an ICD was 6.9%, equating to an NNT (for 45.5 months to postpone one death) of 14.

Use of ICDs in patients with a reduced EF is supported by the findings of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II),[54] an RCT in which 1232 patients with a prior myocardial infarction and an EF of 30% or lower (59% of whom were in NYHA class II or III) were assigned to receive either conventional treatment or conventional treatment plus an ICD. Use of an ICD led to a 31% RRR in mortality (HR 0.69, 95% CI 0.51-0.93; $P=0.016$). Two other trials showed no benefit in patients treated with an ICD early (within 40 days) after myocardial infarction. This is why ICD use in patients with coronary heart disease receives level of evidence A in guidelines, but only in patients 40 days or more after acute myocardial infarction. There is less evidence in patients with nonischemic heart failure, with one moderate-sized trial, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE, n = 458)[55] showing only a nonsignificant trend to a reduction in mortality—hence the evidence level of B in guidelines for patients with nonischemic HF-REF.

The control versus ICD HR in patients with diabetes in SCD-HeFT was 0.95 (95% CI 0.68-1.33), and 0.67 (95% CI 0.50-0.90) in those without. However, in MADIT-II,[56] the HR in patients with diabetes (n = 489) was 0.61 (95% CI 0.38-0.98) and in those without diabetes was 0.71 (95% CI 0.49-1.05), with no evidence of interaction.

ICD implantation should be considered only after a sufficient period of optimization of medical therapy (at least 3 months) and only if the EF remains persistently low.

ICD therapy is not indicated in patients in NYHA class IV with severe, medication-refractory symptoms who are not candidates for cardiac resynchronization therapy (CRT), a ventricular assist device, or cardiac transplantation (because such patients have a very limited life expectancy and are more likely to die from pump failure).

Cardiac Resynchronization Therapy

There is little doubt that patients expected to survive with good functional status for longer than 1 year should receive CRT if they are in sinus rhythm, their EF is low ($\leq$30%), the QRS duration is markedly prolonged ($\geq$150 milliseconds), and an electrocardiogram (ECG) shows a left bundle branch morphology, irrespective of symptom severity.[2] There is less consensus about patients with right bundle branch block or interventricular conduction delay (subgroup analyses suggest little benefit or even harm) and those in atrial fibrillation (AF) (because most trials excluded these patients and because a high ventricular rate will prevent resychronization).[2]

Evidence is available in moderately to severely symptomatic patients. Two key placebo-controlled RCTs—the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial[57] and the Cardiac Resynchronization in Heart Failure (CARE-HF) study[58]—randomized 2333 patients with moderate to severely symptomatic HF (NYHA class III or IV) to either optimal medical therapy or optimal medical therapy plus CRT. Patients in

COMPANION were required to be in sinus rhythm, to have an EF of 35% or lower, to have a QRS duration of at least 120 milliseconds, and to have had a heart failure hospitalization or the equivalent in the preceding year. Patients in CARE-HF were required to be in sinus rhythm and to have an EF of 35% or lower, a QRS duration of 120 milliseconds or longer (if the QRS duration was 120 to 149 milliseconds, other echocardiographic criteria for dyssynchrony had to be met), and an LV end-diastolic dimension of at least 30 mm (indexed to height). Each of these two trials showed that CRT reduced the risk of death from any cause and hospital admission for worsening heart failure—an RRR in death of 24% with a CRT-pacemaker (CRT-P) and of 36% with a CRT-defibrillator (CRT-D) in COMPANION and of 36% with CRT-P in CARE-HF. In CARE-HF, the RRR in HF hospitalization with CRT-P was 52%. The ARR with CRT-D in the composite outcome of CV death or CV hospitalization in COMPANION was 8.6%, equating to an NNT (over a median duration of follow-up of approximately 16 months) to postpone one event of 12. The corresponding figures for CRT-P in CARE-HF (over a mean follow-up of 29 months) were an ARR of 16.6% and an NNT of 6. These trials also showed that CRT improves symptoms, quality of life, and ventricular function. Other trials showed that these devices improve exercise capacity. A subgroup analysis according to diabetes status has been published from both trials (see later).

Evidence is also available in mild to moderately symptomatic patients. Two key placebo-controlled RCTs randomized 3618 patients with mild symptoms (MADIT-CRT[59]—15% NYHA class I and 85% NYHA class II) or moderate symptoms (the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [RAFT][60]—80% NYHA class II and 20% NYHA class III) to either optimal medical therapy plus an ICD, or optimal medical therapy plus CRT-D. Patients in MADIT-CRT were required to have an EF of 30% or lower, to have a QRS duration of 130 milliseconds of longer, and to be in sinus rhythm. Patients in RAFT were required to have an EF of 30% or lower and a QRS duration of 120 milliseconds or longer (13% of enrolled patients had AF with a well-controlled ventricular rate). Each of these two trials showed that CRT reduced the risk of the primary composite endpoint of death or heart failure hospitalization ("heart failure event" in MADIT-CRT)—RRR of 34% in MADIT-CRT and 25% in RAFT. There was a 25% reduction in all-cause mortality in RAFT ($P=0.003$), but mortality was not reduced in MADIT-CRT. It is important to note that these benefits were in addition to those gained from conventional treatment, including a diuretic, digoxin, an ACE inhibitor, a beta blocker, an MRA, and an ICD. The ARR in the primary composite mortality-morbidity endpoint in MADIT-CRT was 8.1%, equating to an NNT (for an average of 2.4 years to postpone one event) of 12. The equivalent figures for RAFT were ARR 7.1% and NNT 14 (over an average of 40 months). These trials also showed that CRT improves symptoms, quality of life, and ventricular function. Both MADIT-CRT and RAFT showed a significant treatment-by-subgroup interaction whereby QRS duration modified the treatment effect (CRT appeared more effective in patients with a QRS of 150 milliseconds or longer), and patients with left bundle branch block also seemed to obtain more benefit than those with right bundle branch block or an interventricular conduction defect.

The COMPANION, CARE-HF, and MADIT-CRT investigators have each published subgroup analyses in relation to the baseline diabetes status of the patients in their trials.

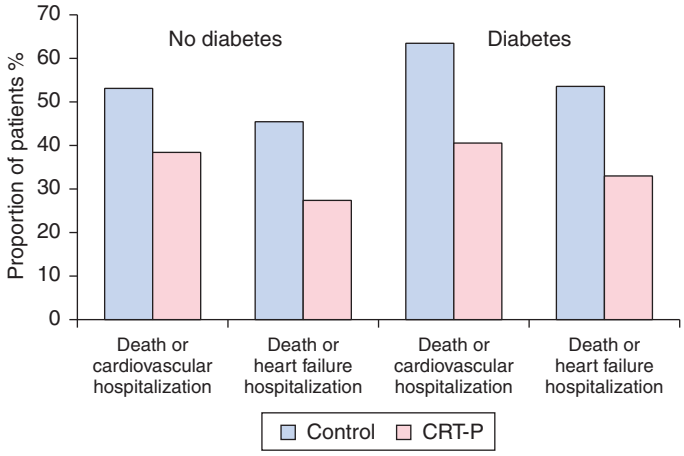


FIGURE 26-7 Effect of CRT in patients with HF-REF in the CARE-HF trial.

In the two trials in patients with moderate to severe symptoms, CRT was at least as effective in reducing death and hospitalization in patients with diabetes as in those without (**Fig. 26-7**). In particular, among patients with diabetes, CRT reduced the risk of death from any cause by 37% in COMPANION.[61] In COMPANION, CRT also improved 6-minute walk distance, NYHA class, and quality-of-life score (all significantly), compared with optimal medical therapy, in patients with diabetes. Similar benefits were reported in CARE-HF.[62]

There were 552 patients with diabetes, HF-REF, a QRS duration of 130 milliseconds or longer, and mild symptoms in MADIT-CRT.[63] CRT-D treatment, compared with optimal medical therapy and an ICD, led to a significant reduction in the risk of the primary endpoint of death from any cause or a heart failure event in patients with diabetes (adjusted HR 0.56, 95% CI 0.40-0.79; $P<0.001$) and in those without (0.67, 95% CI 0.51-0.87; $P=0.003$). The unadjusted Kaplan-Meier estimate of the NNT over 2 years to prevent one death or heart failure event was 6.9 (95% CI 4.5-15.0%) for patients with diabetes compared with 17.5% (10.0-73.5%) for patients without diabetes ($P=0.054$).

Although not published as a separate paper, subgroup analysis of RAFT showed that the benefit of CRT-D was similar in patients with and without diabetes.[60]

Patients with diabetes did not experience a higher rate of complications related to device implantation, including infection. There were similar CRT-related improvements in LV volumes and EF in those with and without diabetes.

Coronary Artery Bypass Grafting

Coronary revascularization, preferably surgical revascularization (see also **Chapter 18**), is indicated for the relief of angina pectoris in patients with HF-REF (and HF-PEF) and diabetes. Surgical coronary revascularization is indicated for prognostic reasons in other patients with severe coronary artery disease (CAD), particularly those with three-vessel disease or left main coronary artery stenosis.[2] The detailed indications for coronary revascularization are covered elsewhere (see **Chapters 17** and **18**). This section focuses on recent developments relevant to heart failure.

The Surgical Treatment for Ischemic Heart Failure (STICH)[64] trial addressed the broader role of surgical revascularization in patients with HF-REF and less severe CAD. Patients with an EF of 35% or lower and CAD who were suitable for surgery were randomized to coronary artery bypass



grafting (CABG) plus medical therapy or medical therapy alone. The patients enrolled were young (average age 60 years), predominantly male (88%), and in NYHA class I (11%), II (52%), or III (34%). Their Canadian Cardiovascular Society angina class was 0 in 36%, I in 16%, II in 43%, III in 4%, and IV in 1%. Most patients had two-vessel (31%) or three-vessel (60%) CAD, and 68% had a severe proximal left anterior descending coronary artery stenosis; very few (2%) had a left main coronary artery stenosis. The primary outcome (all-cause death) was not reduced by CABG. CABG did, however, reduce the secondary outcomes of CV death (RRR 19%) and death from any cause or CV hospitalization (RRR 26%).

The STICH investigators reported a subgroup analysis by diabetes status for the outcome of death from any cause. For the 478 patients with diabetes, the control versus CABG HR was 0.92 (95% CI 0.70-1.22), and for the 734 patients without diabetes HR was 0.83 (95% CI 0.65-1.05); interaction $P=0.6$.

This trial may therefore extend the indication for CABG to "STICH-like" patients with two-vessel CAD, including a left anterior descending coronary artery stenosis, who are otherwise suitable for surgery and expected to survive for longer than 1 year with good functional status. Many physicians and surgeons also assess "myocardial viability" in addition to coronary anatomy before making a decision about the potential benefits and risks of coronary revascularization (see **Chapters 17** and **18**).

Ventricular Assist Devices and Transplantation

Microvascular complications other than nonproliferative retinopathy are usually considered a relative contraindication to both cardiac transplantation and mechanical circulatory support.[65,66] Patients with advanced diabetes have poorer long-term survival than other candidates for transplantation, and this also seems to be the case with mechanical circulatory support. Good glycemic control (glycated hemoglobin below 7.5%) should be established before surgery.[65,66]

EXERCISE PRESCRIPTION

Meta-analyses of small studies have shown that physical conditioning by exercise training improves exercise tolerance and health-related quality of life and possibly reduces hospitalization in patients with heart failure. A single large trial—Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)[66]—investigated the effects of exercise training in 2331 relatively young (mean age 59 years) medically stable patients with mild to moderately severe symptoms (NYHA class II 63% and class III 35%) and an EF of 35% or lower. The intervention comprised 36 supervised sessions in the initial 3 months followed by home-based training.[67] The median follow-up was 30 months. In an adjusted analysis, exercise training led to a 7% unadjusted ($P=0.13$) and 11% adjusted ($P=0.03$) reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization. There was also a 13% unadjusted ($P=0.06$) and 15% adjusted ($P=0.03$) RRR in a secondary composite outcome of CV death or heart failure hospitalization. There was no reduction in mortality, and there were no safety concerns. Adherence to exercise declined substantially after the period of supervised training.

Collectively, the evidence suggests that physical training is beneficial in heart failure, although typical elderly patients were not enrolled in many studies and the optimum exercise prescription is uncertain. Furthermore, the only large trial, HF-ACTION, showed a borderline treatment effect that was obtained only with a very intensive intervention that may not be practical to deliver in every center.

Although 32% of patients in HF-ACTION had diabetes, the effect of the intervention has not been reported in this subgroup.

TREATMENT OF DIABETES IN PATIENTS WITH HEART FAILURE

The overall goal of glucose management is to prevent the development of microvascular and macrovascular complications while avoiding treatment side effects. Control of glycemia is more effective at reducing microvascular than macrovascular complications. Current guidelines focus on multiple risk factor modification to reduce global CV risk, with lifestyle modification and pharmacologic therapy to improve glycemic control. Most clinical trials examining the pharmacologic treatment of diabetes have disappointingly excluded patients with heart failure. Our knowledge of the treatment of diabetes in heart failure is limited to that extrapolated from trials in patients with diabetes but without heart failure or from observational studies.

There are a number of different classes of glucose-lowering medications, each with a different mechanism of action. Initial treatment of diabetes is with lifestyle modification plus medication monotherapy. Patients who fail to reach glycemic targets are moved on to two medication combinations, then three medication combinations, then more complex insulin regimens. Heart failure is an insulin-resistant state, and control of glycemia can be very difficult. Patients may not respond to oral glucose-lowering medications and even large doses of insulin may result in only limited reductions in glycemia. We will deal with each of the main medication classes in turn and summarize the current evidence for each in patients with heart failure.

Metformin

Though it previously was, metformin is a biguanide. It appears to mediate its effect on blood glucose via a number of different mechanisms: reducing hepatic gluconeogenesis, increasing insulin sensitivity, increasing peripheral glucose uptake, and decreasing gut absorption of glucose. Metformin is considered first-line therapy in patients with diabetes, particularly in obese patients, because it slightly reduces weight, and in a small subgroup of the United Kingdom Prospective Diabetes Study (UKPDS) it was associated with a reduction in myocardial infarctions when started as initial monotherapy.[68,69]

Though it previously was, metformin is no longer contraindicated in patients with heart failure (see also **Chapter 17**). In 2006, the U.S. Food and Drug Administration (FDA) withdrew its previous recommendation that metformin should not be used in patients with heart failure, allowing product label modification for all metformin products. Metformin had been a victim of unwarranted "guilt by association." An earlier member of the biguanide family called *phenformin* was withdrawn from the market in the 1970s following its association with lactic acidosis. Two large observational studies in patients with heart failure and diabetes and one meta-analysis demonstrated no link between metformin and lactic acidosis.[70–74]

There is no large RCT examining the use of metformin in patients with diabetes and heart failure. Observational studies suggest benefit rather than harm. Two large retrospective cohort studies in the United States and Canada have examined the use of metformin in patients with both diabetes and heart failure.[72,74] Both used multivariable analyses to adjust for confounding variables. The Canadian cohort study examined outcomes in 1833 patients and demonstrated that use of metformin either as monotherapy or combined with a sulfonylurea was associated with a lower 1-year mortality when compared with sulfonylurea monotherapy.[72] The U.S. study examined 16,417 people hospitalized with heart failure. In that study, use of metformin was associated with a lower 1-year mortality when compared with treatment with insulin or sulfonylurea (24.7% versus 36%, $P < 0.0001$).[74] Metformin was also associated with a lower all-cause hospitalization and heart failure hospitalization. The use of metformin in diabetic patients with heart failure has been associated with better outcomes in several other cohort studies from the United States, the United Kingdom, Spain, and Denmark.[70–74]

Although metformin is no longer considered to be contraindicated in patients with heart failure, there are still certain patient subgroups in whom its use is contraindicated (see also **Chapter 17**).[75,76] It should not be used in patients at increased risk of developing lactic acidosis—that is, those with significant renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL in men or ≥1.4 mg/dL in women or reduced creatinine clearance) or in patients with acute heart failure or myocardial infarction, shock, or sepsis. If a patient is admitted to the hospital with acute heart failure, metformin should be temporarily withheld until his or her condition has stabilized.

Although metformin does not appear to be harmful in patients with heart failure and may even be associated with mortality benefit, we must stress that this impression is solely based on observational studies, which are often misleading. It is possible that metformin could simply have been a marker for patients with less severe disease. Despite this caveat, for all patients with type 2 diabetes, whether or not that patient has heart failure, metformin should be considered as the first-line medication to treat hyperglycemia. In routine clinical practice, however, its use is limited by a high incidence of gastrointestinal side effects.

Sulfonylureas

Sulfonylureas act by increasing insulin release from the beta cells of the pancreas (see also **Chapter 17**). Because heart failure is an insulin-resistant state, this is not an attractive method of achieving blood glucose control, as it may have limited efficacy. Despite this, sulfonylureas remain the most commonly prescribed glucose-lowering medications in patients with heart failure.

No randomized trial has examined the use of a sulfonylurea in patients with both heart failure and diabetes. Existing evidence is primarily from retrospective cohort studies, and this does not suggest that sulfonylureas are harmful in patients with heart failure. A large retrospective observational U.S. cohort study involving more than 16,000 patients with diabetes and heart failure found no link between sulfonylurea use and mortality (HR 0.99 (95% CI 0.91-1.08).[74] A Canadian retrospective cohort study of patients with diabetes and heart failure compared metformin use with sulfonylurea use.[72] One-year mortality in patients treated with metformin was lower than in patients treated with sulfonylureas (adjusted HR 0.66 (95% CI 0.44-0.97). This suggests that use of a sulfonylurea should be considered only if metformin is contraindicated or not tolerated, or when being given in combination with metformin.

Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists (see also **Chapter 17**). They improve insulin sensitivity, lipid profile, and blood glucose control. They cause weight gain and fluid retention by increasing fluid reabsorption in the renal collecting duct, which is of concern for patients with heart failure. This is particularly seen when TZDs are used in conjunction with insulin. In patients with diabetes, it has also been suggested that rosiglitazone may increase the risk of myocardial infarction, although this association has not been proven definitively.[72] Several RCTs, cohort studies, and meta-analyses have demonstrated that TZDs increase the incidence of fluid retention and heart failure in patients with diabetes.[77–79] The extent to which TZDs cause simple fluid retention or symptomatic heart failure is not clear from the literature. Most of the trials did not measure LV function or natriuretic peptides prospectively. Randomized trials suggest that although TZDs have no effect on LV function they may be associated with an increase in B-type natriuretic peptide.[80,81] It is likely that at least in a proportion of patients, TZDs cause fluid retention that converts a patient with subclinical LV dysfunction into one with symptomatic heart failure.

Most RCTs examining the safety and efficacy of TZDs in diabetes have excluded patients with heart failure. A systematic review and meta-analysis on the subject suggests that treatment with TZDs leads to an increased risk of heart failure hospitalization (pooled odds ratio 1.13 [95% CI 1.04-1.22]).[82] In the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial, heart failure hospitalization in the rosiglitazone group had the same adverse prognostic consequence as in the placebo group.[78]

According to the FDA, TZDs are contraindicated in patients with symptomatic heart failure (NYHA III or IV). Caution is also advised in their use in patients with NYHA class I or II heart failure. Our view is that these agents should not be used in patients with heart failure or LV systolic dysfunction.

Insulin

Insulin is indicated when oral treatments have failed to provide adequate glycemic control (see also **Chapter 17**). Insulin has been shown to dilate arteries in skeletal muscle in patients with heart failure, so some have postulated that it may be an attractive glucose-lowering medication for this patient group. Insulin, however, causes weight gain and increases sodium retention, which is a concern, and there are occasional case reports of heart failure in patients starting insulin treatment. However, the CV safety of insulin glargine was tested in the recent Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial in people aged 50 years or older with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes in addition to other CV risk factors. Overall, 88% of patients in ORIGIN had diabetes and their condition had been present for a mean duration of



5.4 years; 6% had a new diagnosis and 23% were receiving no pharmacologic therapy before randomization. The median trial follow-up was 6.2 years. The rate of hospital admission for heart failure was 0.85/100 patient-years in the insulin group compared with 0.95/100 patient-years in the control group. Although these findings are reassuring, patients in ORIGIN had diabetes for a relatively short duration (or no diabetes at all), and those with longer-duration diabetes are at greater risk of heart failure and may be at greater risk of medication-induced heart failure.[83]

No large RCT has specifically examined the effect of insulin in patients with heart failure. Several post hoc analyses from clinical trials and cohort studies have identified that patients treated with insulin are at greater risk of death than patients treated with other glucose-lowering medications.[84,85] It is likely that insulin is a marker for diabetes of greater duration and the presence of extensive macrovascular disease rather than insulin being directly responsible for this association.

Despite the association of insulin with poorer outcomes in patients with heart failure, this does not mean that insulin should not be used. Prospective trials would be welcome.

Modulators of the Incretin System

In recent years a large number of new compounds have been developed for the treatment of diabetes (see also **Chapter 17**). For patients with both heart failure and diabetes, the most interesting group of compounds consists of modulators of the incretin system. Incretins are gut peptides excreted in response to a meal that act to reduce postprandial hyperglycemia. Glucagon-like peptide 1 (GLP-1) is an incretin peptide that stimulates insulin secretion by the beta cells of the pancreas in a glucose-dependent fashion—that is, it stimulates insulin secretion only if blood glucose crosses a threshold level. It also acts to decrease glucagon secretion, delay gastric emptying, and suppress appetite. Patients with type 2 diabetes have reduced GLP-1 secretion in response to a meal. Incretin peptides are rapidly broken down in the body by dipeptidyl peptidase 4 (DPP-4). Currently available compounds acting on the incretin system are the oral inhibitors of DPP-4, sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, which act to increase endogenous GLP-1, and injectable GLP-1 receptor agonists exenatide, liraglutide, albiglutide, and lixisenatide. DPP-4 inhibitors and GLP-1 receptor agonists reduce hemoglobin A1c (HbA1c) without increasing the risk of hypoglycemia and are generally well tolerated by patients. GLP-1 receptor agonists appear to be marginally more efficacious at reducing HbA1c and have the added benefit of promoting weight loss, whereas DPP-4 inhibitors are weight neutral.

Modulators of the incretin system are of particular interest in patients with heart failure, given the potentially beneficial effects of GLP-1 on the CV system. Small studies in both animals and humans with heart failure indicate that short-term treatment with GLP-1 can lead to improvements in ventricular function and hemodynamics.[86] In one recent small study, 6 hours of intravenous exenatide increased cardiac index, reduced pulmonary capillary wedge pressure, and was reasonably well tolerated in patients with type 2 diabetes and congestive heart failure (CHF) (NYHA class III or IV).[87] It should be noted, however, that heart rate increased with exenatide, generally an unfavorable finding in heart failure.

The first long-term outcome study with an incretin-based therapy used the DPP-4 inhibitor saxagliptin. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis In Myocardial Infarction 53 (SAVOR-TIMI 53) trial randomized 16,492 patients with type 2 diabetes and established CV disease, or risk factors for CV disease, who were followed for a median of 2.1 years. Compared with placebo, saxagliptin increased the risk of hospitalization for heart failure (3.5% versus 2.8%, $P=0.007$). More details regarding the type of heart failure patients developed and the outcomes in these patients are awaited.[88] A second trial, Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE), evaluated the CV safety of a second DPP-4 inhibitor in patients with type 2 diabetes and a recent acute coronary syndrome. In EXAMINE, patients were randomly assigned to receive alogliptin or placebo in addition to standard-of-care medications for diabetes and CV disease. A total of 5380 patients were followed for a median of 18 months. Although the occurrence of heart failure was not reported in the primary publication from this trial, data on this outcome were presented at the 2013 congress of the European Association for the Study of Diabetes.[89] The composite outcome of CV death or heart failure hospitalization occurred in 201 alogliptin-treated patients (7.4%) and 201 placebo patients (7.5%) (HR 0.98, 95% CI 0.82-1.20). The components of this composite (first events only) included 95 CV deaths (3.5%) and 106 heart failure hospitalizations (3.9%) in the alogliptin group and 112 (4.2%) and 89 (3.3%), respectively, in the placebo group (CV death HR 0.84, 95% CI 0.64-1.10; and heart failure hospitalization HR 1.19, 95% CI 0.90-1.58). Although even less is known about heart failure in this trial, the HR and 95% CI for heart failure hospitalization appear consistent with the findings of SAVOR-TIMI 53.

Whether this completely unexpected finding reflects the play of chance, is medication specific, is a DPP-4 class-effect, or even is an issue for other incretin-based therapies (e.g., GLP-1 analogues) is unknown at this point. The findings are clearly at odds with the observation that heart failure is characterized by high DPP-4 activity and that reducing this activity with DPP-4 inhibitors has beneficial effects in experimental models of heart failure. Clearly, much more information is needed on the safety of incretin-based therapies in patients with diabetes and heart failure.[90-94]

Other Glucose-Lowering Medications

Alpha-glucosidase inhibitors inhibit the enteric enzyme alpha-glucosidase, preventing the breakdown of complex carbohydrates to glucose (see also **Chapter 17**). This leads to a reduction in blood glucose levels. They are associated with modest reductions in HbA1c, and the reduction in glycemia is less than with other medication classes. They can be used as monotherapy or in combination with other glucose-lowering medications. Frequent gastrointestinal side effects limit the use of these medications in the United States and Europe, but they are widely used in Asia. There is no evidence available examining their pros and cons in patients with diabetes and heart failure.

A sustained-release formulation of bromocriptine has been approved for use in diabetes by the FDA. The mechanism of reduction in HbA1c is not well understood; the medication may act centrally to reduce insulin resistance. In a 1-year safety study it was demonstrated to reduce CV events.[95] Exclusion criteria included NYHA class III or IV heart failure, and

separate data have not been provided for patients with heart failure at baseline. The number of total events in the study was small, and the findings require confirmation in a longer study.

Colesevelam, a bile acid sequestrant, is associated with modest reductions in HbA1c and so far has limited use as a treatment for type 2 diabetes. Pramlintide, an amylin mimetic, is an injected therapy that reduces glucagon secretion in type 1 diabetes and has to given along with insulin. Reductions in HbA1c are also modest, with nausea and vomiting as side effects, and overall use has been limited. There are no specific data on use in diabetic patients with heart failure for either of these treatments.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a new class of medications that inhibit the reabsorbtion of glucose in the kidney, promoting glycosuria. This leads to a decrease in blood glucose levels and a reduction in weight. A slight reduction in blood pressure has been observed and may be related to renal sodium loss. These agents can be used as monotherapy or in combination with other glucose-lowering medications including in combination with insulin. There is currently no evidence available examining their pros and cons in patients with diabetes and heart failure. Theoretically, the slight loss of fluid might improve symptoms of heart failure, whereas caution might be required in fluid-depleted patients.

Intensity of Glucose-Lowering

Three large clinical trials set out to address whether or not more intensive glycemic control versus contemporary standard care would reduce the risk of CV events in patients with type 2 diabetes, and their results have recently been published: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), and VADT (Veteran Affairs Diabetes Trial) (see also **Chapter 17**).[96-98] All three studies demonstrated that intensive reduction of HbA1c (to levels below currently recommended) did not translate into reductions of CV outcomes. In fact, ACCORD was stopped early because of an excess number of deaths in the intensive therapy group. How does this new evidence apply to patients with both heart failure and diabetes? It should be noted that few patients in these studies had heart failure; in ACCORD only 4.8% had a history of heart failure. Also, the pharmacologic strategies used in these studies may not have been the ideal choice for heart failure patients; in the ACCORD trial there was very high use of TZDs, and in the ADVANCE trial there was much greater use of insulin sulfonylureas than metformin. Meta-analysis of intensive glycemic control has shown no impact on the risk of heart failure in type 2 diabetes, but longer studies or follow-up may be required to show reductions in heart failure outcomes, and off-target effects of the treatments used, such as fluid retention with TZDs,[98] may have offset beneficial effects of improved glycemic control. Prospective clinical trials in patients with both diabetes and heart failure, using agents with favorable CV risk profiles, are warranted.

SUMMARY

The evidence presented here regarding the treatment of diabetes in patients with heart failure must not be overinterpreted. These results are not based on evidence from randomized controlled trials specifically designed to assess outcomes in patients with diabetes and heart failure. They are predominantly based on data from retrospective cohort studies. From the available evidence, metformin appears to be the initial glucose-lowering medication of choice in patients with type 2 diabetes and heart failure. After metformin, physicians must weigh the pros and cons of alternative agents and tailor therapy to the individual. The future may be brighter for glucose management, with many new agents in development. Some of these are reported to have beneficial effects on myocardial metabolism. The FDA now requires these new agents to undergo rigorous prospective assessment to ensure CV safety.

Large numbers of patients worldwide have both diabetes and heart failure. The two conditions when present together lead to significantly increased morbidity and mortality. Unfortunately, most clinical trials examining diabetic treatments have excluded patients with heart failure. The management of diabetes in patients with heart failure must follow standard guidelines for both heart failure and diabetes. Physicians must be aware that metformin is not contraindicated in patients with heart failure, and it should be considered as first-line therapy. Clinical trials examining the safety and efficacy of novel glucose-lowering agents in patients with heart failure are under way.

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PART VI

OTHER DIABETES-RELATED CARDIOVASCULAR CONSIDERATIONS

27 Peripheral Artery Disease in Diabetes

Neil J. Wimmer and Joshua A. Beckman

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Peripheral artery disease (PAD) is generally defined as partial or complete obstruction of one or more arteries affecting the lower extremities and is usually caused by atherosclerosis. Symptoms of PAD include pain with ambulation, resulting from an inadequate blood supply relative to demand in the lower extremities, termed *intermittent claudication*. In severe cases, symptoms occur at rest and tissue ischemia may lead to ulceration or amputation. PAD may also be asymptomatic, but the association of PAD with other comorbid cardiovascular disease often results in an increased risk of mortality. Patients with diabetes are among those most likely to develop PAD and also among those most likely to develop complications resulting from both disease processes.

This chapter provides a framework for the diagnosis and management of patients with PAD, focusing on the overlap and special characteristics of patients with concomitant diabetes.

EPIDEMIOLOGY AND PROGNOSIS OF PERIPHERAL ARTERY DISEASE AND DIABETES—OVERLAPPING EPIDEMICS

The reported prevalence of PAD varies as a function of the population tested, the diagnostic method used, and whether symptoms are included to derive estimates. The ankle-brachial index (ABI) is the most commonly used noninvasive measurement in epidemiologic studies and is described in more detail later. The ABI is the ratio of the ankle to the brachial systolic blood pressure. For intermittent claudication, prevalence estimates range from below 2% to as high as 12%, whereas rates of noninvasively defined disease based on the ABI range from 3% to 33%.[1,2] The prevalence of PAD increases with age, with rates of approximately 4% documented in those 40 years and older compared with rates of 13% to 15% among those 65 years of age and older[3–5] (**Fig. 27-1**). Only a small proportion of those with ABI-defined PAD have claudication, with estimates ranging from approximately 10% to 30%. The prevalence of PAD increases with age[3,6] (**Fig. 27-2**). There is less information about the true incidence of critical limb ischemia or amputation, but estimates suggest that 400 to 450 individuals per million population are affected with ischemia and approximately 112 to 250 individuals per million population require amputation.[6]

Major risk factors for PAD overlap with, but are not identical to, those for coronary artery disease (CAD) and cerebrovascular disease. It is important to note that diabetes, smoking, older age, elevated triglyceride concentrations, and elevated systolic blood pressure are particularly potent risk factors for PAD.[5] Data from the National Health and Nutrition Examination Survey (NHANES) suggest that cigarette smoking and diabetes are the most potent risk factors associated with the development of PAD, with odds ratios for the development of PAD of 4.5 and 2.7, respectively. In the Framingham study, the presence of diabetes increased the risk of intermittent claudication by 3.5-fold in men and 8.6-fold in women.[7] Even in those without frank diabetes, insulin resistance has also been linked to the development of PAD.[8]

The duration and severity of diabetes correlates with the incidence and extent of PAD. In a prospective cohort study, Al-Delaimy and colleagues[9] found a strong association between the duration of diabetes and the risk of developing PAD. The association was particularly strong among men with hypertension or who were current smokers. Adler and colleagues[10] estimated the prevalence of PAD up to 18 years after the diagnosis of diabetes in almost 5000 patients from the United Kingdom Prospective Diabetes Study (UKPDS). They demonstrated a higher prevalence of PAD in those with a longer duration of diabetes. The degree of diabetic glycemic control is an independent risk factor for PAD; with every 1%

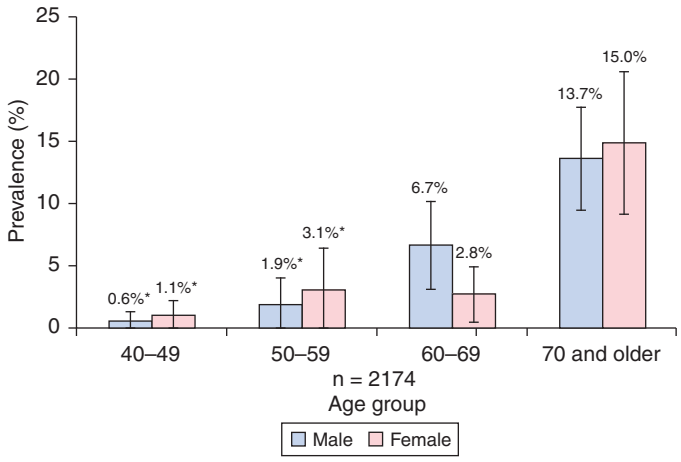


FIGURE 27-1 PAD prevalence and age from the National Health and Nutrition Examination Survey (NHANES).[5] *(Modified from Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000,* Circulation *110:738-743, 2004.)*

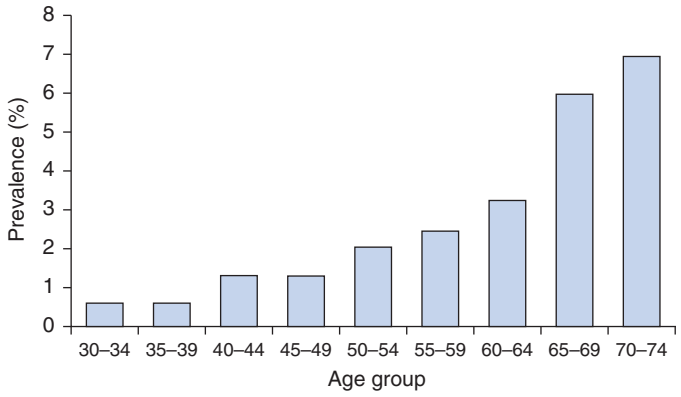


FIGURE 27-2 The prevalence of claudication with age. From TransAtlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC II).[6] *(Modified from Norgren L, Hiatt WR, Dormandy JA, et al: Inter-society Consensus for the Management of Peripheral Arterial Disease [TASC II],* Eur J Vasc Endovasc Surg *2007;33[Suppl 1]:S1-S75, 2007.)*

increase in glycosylated hemoglobin (HbA1c), the risk of PAD has been shown to increase by 28%.[11]

Furthermore, patients with diabetes and PAD are more likely to present with an ischemic ulcer or gangrene than patients without diabetes, increasing the risk of lower-extremity amputation.[12] Faglia and colleagues observed a positive trend between PAD severity and amputation rates in patients with diabetes.[13] Individuals with diabetes are approximately 15 times more likely to have an amputation than those without diabetes,[14] and an annual amputation incidence rate of 0.6% has been reported in diabetic patients.[15,16] Patients with diabetes often have extensive and severe PAD and a greater propensity for arterial calcification.[17,18] Involvement of the femoral and popliteal arteries often resembles that of nondiabetics, but distal disease affecting the tibial and peroneal arteries occurs more frequently in diabetics.[12]

CLINICAL PRESENTATION, DIAGNOSIS, AND NATURAL HISTORY OF PERIPHERAL ARTERY DISEASE IN DIABETES

The hallmark features of clinical PAD include intermittent claudication and rest pain. The location of the symptoms often relates to the site of the most proximal stenosis. In general, buttock, hip, or thigh claudication typically occurs in patients with aortic or iliac stenoses. Calf claudication characterizes femoral or popliteal involvement. Ankle or foot claudication occurs in patients with tibial or peroneal disease. Claudication symptoms should be brought on by exertion and should resolve within minutes after cessation of effort. Leg pain that occurs at rest, such as nocturnal cramping in the calf or thigh, should not be confused with claudication.

Symptoms may occur at rest in patients with critical limb ischemia. Typically, patients complain of paresthesias or pain in the foot or toes of the affected limb. This discomfort worsens with limb elevation and often improves when the limb is lowered, as would be expected because of the increased perfusion pressure to the distal limb by the effect of gravity. The pain can be particularly severe at sites of skin breakdown, and often the skin is exquisitely sensitive to light touch. These symptoms may be absent, however, in diabetic patients with significant peripheral neuropathy, who may have important limb ischemia but experience few symptoms.

A complete cardiovascular physical examination is necessary to detect all the findings of PAD in diabetic patients. Pulse abnormalities and bruits increase the likelihood of PAD.[19] The legs of patients with chronic aortoiliac disease may demonstrate muscular atrophy. Hair loss, thick or brittle toenails, and smooth and shiny skin on the legs can also indicate PAD. Patients with severe limb ischemia often have cool skin and may have petechiae, cyanosis or pallor, dependent rubor, skin fissures, ulceration, or gangrene. Ulcers that result from PAD often have a pale base with irregular borders and usually involve the tips of the toes, the heel of the foot, or other sites that bear chronic pressure (**Fig. 27-3**). Overall, physical examination has a low sensitivity but high specificity for PAD.[20]

The clinical stage of symptomatic PAD can be classified according to the Fontaine or Rutherford scoring systems.[6,21] Fontaine stage I represents those who have PAD but are asymptomatic. Stages IIa and IIb include patients with mild and moderate-to-severe intermittent claudication. Patients with ischemic rest pain are classified as stage III, and those with ulceration or gangrene are stage IV. In the Rutherford classification, asymptomatic patients are classified as category 0. Patients with mild claudication are category 1. Patients with moderate claudication are category 2, and patients with severe claudication are category 3. Patients



FIGURE 27-3 A typical nonhealing arterial ulcer.

TABLE 27-1 Clinical Classification Schemes for Peripheral Artery Disease

FONTAINE CLASSIFICATION		RUTHERFORD CLASSIFICATION		
Stage	Clinical Description	Grade	Category	Clinical Description
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-to-severe claudication	I I	2 3	Moderate claudication Severe claudication
III	Rest pain	II	4	Rest pain
IV	Ulceration or gangrene	III IV	5 6	Minor tissue loss Ulceration or gangrene

Data from White CJ, Gray WA: Endovascular therapies for peripheral arterial disease: an evidence-based review, *Circulation* 116:2203-2215, 2007.

with rest pain are category 4. Patients with minor tissue loss, ulceration, or gangrene are categories 5 and 6 (**Table 27-1**).

The main reasons to diagnose PAD in diabetic individuals are to initiate therapies that decrease the risk of atherothrombotic events, to improve the overall quality of life, and to decrease disability. A diagnosis of PAD indicates the presence of systemic atherosclerosis that confers additional cardiovascular risk to the patient with diabetes, which gives further impetus to aggressively manage vascular risk factors in this high-risk group. Although the physical examination provides important information, additional noninvasive testing is necessary to ensure the diagnosis of PAD. The ABI is a reproducible and reasonably accurate measurement for the detection of PAD. The American Heart Association recently published a consensus scientific statement regarding use of the ABI and suggested standard definitions and interpretation.[22] As mentioned earlier, the ABI is defined as the ratio of the ankle systolic blood pressure divided by the brachial systolic blood pressure. The ABI is normally between 1.00 and 1.40.[22,23] In PAD, the ankle systolic blood pressure is less than the brachial systolic blood pressure, and the ABI is reduced to below 1.00. PAD is defined as an ABI of 0.90 or lower, with values from 0.91 to 1.00 classified as borderline.[22,24] Lower ABI values indicate more severe PAD. Patients with symptoms of leg claudication often have ABIs from 0.5 to 0.8, and patients with critical limb ischemia usually have an ABI below 0.5. The ABI has been shown to correlate inversely with walking distance and walking speed (**Fig. 27-4**). For example, less than 40% of patients with an ABI below 0.4 can complete a 6-minute walking test.[25] One limitation of the ABI in patients with diabetes, however, is that leg blood pressure recordings cannot be reliably interpreted in patients with calcified vessels because these vessels are not reliably compressed during inflation of the blood pressure cuff. Because diabetic patients are more likely than nondiabetics to have arterial calcifications, ABI measurements in certain individuals can be difficult to interpret, and other noninvasive tests, such as a toe-brachial index, should be used to make the diagnosis. The diagnostic measurement of the ABI for the detection of lower-extremity PAD varies according to the population studied, the cutoff threshold, and the comparison gold standard test (invasive angiography or duplex ultrasound). The sensitivity and specificity of the ABI range from 0.17 to 1.0 and from 0.8 to 1.0, respectively.[22] Overall, lower sensitivities are reported in diabetic patients.[26–28]

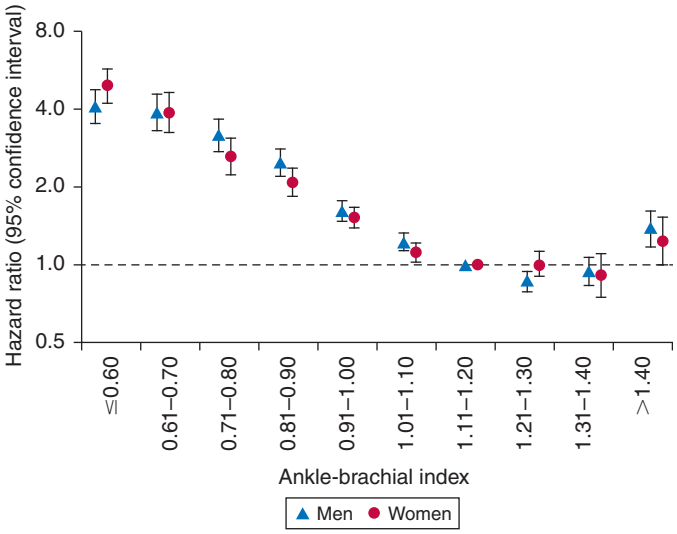


FIGURE 27-4 Ankle-brachial index (ABI) and overall mortality in men and women.[127] *(Modified from Fowkes FG, Murray GD, Butcher I, et al: Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality: a meta-analysis,* JAMA *300:197-208, 2008.)*

The American Diabetes Association (ADA) consensus statement recommends that a screening ABI be performed in all diabetic individuals older than 50 years or in anyone with symptoms consistent with PAD.[29] For the general, nondiabetic population, screening ABI testing is recommended at age 65, or at age 50 in individuals with a history of tobacco smoking.[24] In general, PAD is underdiagnosed in the primary care setting.[30] A large-scale PAD screening study demonstrated that only one third of patients with documented PAD had classical claudication symptoms.[20] These data suggest that classic symptoms are inadequate in determining a person's health status with regard to PAD. Particularly in diabetic patients with peripheral neuropathy, ABI screening of asymptomatic individuals represents an important tool in diagnosing PAD and allowing for an appropriately tailored strategy for therapeutic decisions.

Recent data from the National Health and Nutrition Examination Study[31] demonstrate that there are significant treatment gaps, even once patients have been identified as having abnormal ABI measurements. For example, among patients with ABI-documented PAD, statin use was reported in only 30.5% ± 2.5%, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) use in 24.9% ± 1.9%, and aspirin use in 35.8% ± 2.9%. These numbers correspond to estimates of 5.0 million adults with PAD not taking statins, 5.4 million not taking ACE inhibitors or ARBs, and 4.5 million not taking aspirin. In the same study, these treatment gaps were shown to be associated with elevated mortality rates even after adjustment for other important confounding factors.

In a patient with confirmed PAD for whom further investigation is required, usually at a time when revascularization is considered, there are other modalities available for investigating the extent and nature of the PAD. Segmental pressure and pulse volume recordings are both noninvasive hemodynamic studies that aid in the localization of arterial occlusive disease.[32] Other noninvasive imaging techniques, including magnetic resonance angiography (MRA) and computed tomographic angiography (CTA), or duplex ultrasonography can provide more precise anatomic information for revascularization planning purposes. Conventional,

contrast-based angiography can still be useful, particularly when other modalities have left doubts as to the diagnosis.

Overall, patients with PAD have an increased risk of adverse cardiovascular events, as well as impaired quality of life, and an increased risk of limb loss. In addition, patients with PAD and concomitant diabetes are at risk for higher cardiovascular and cerebrovascular event rates than comparable nondiabetics.[29] The combination of PAD and diabetes causes most nontraumatic lower-extremity amputations in the United States.[33] The relative risk for lower-extremity amputation in patients with diabetes was 12.7 (95% confidence interval [CI] 10.9-14.9) compared with 23.5 (95% CI 19.3-29.1) for diabetic patients in the Medicare population.[33]

RISK FACTOR IDENTIFICATION, LIFESTYLE MODIFICATION, AND PHARMACOTHERAPY

Once diabetic individuals with PAD have been identified, the aim of medical management is to aggressively modify cardiovascular risk factors for the prevention of adverse cardiovascular events and to relieve symptoms related to PAD to improve functional status and quality of life. These two goals should be addressed simultaneously in every patient.

Lowering Cardiovascular Morbidity and Mortality

The risk factors for PAD are identical to those for other forms of atherosclerotic vascular disease, and PAD is similarly associated with an increased risk of coronary, cerebrovascular, and renovascular disease. As a result, PAD is considered a coronary heart disease equivalent, elevating it to the highest category of cardiovascular risk.[34] The 2005 American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines (with the 2011 focused update), the 2003 ADA consensus statement, and the 2007 TransAtlantic Inter-Society Consensus (TASC II) document on the management of PAD recommend smoking cessation, lipid-lowering therapy with statins, and the treatment of diabetes and hypertension.[24,29,35,36] Data from a Dutch prospective cohort study of 2420 patients with PAD (ABI 0.90 or lower) support these conclusions and demonstrate that a comprehensive approach to risk factor modification can have additive benefits.[37] In this study, Feringa and colleagues demonstrated that after adjustment for risk factors and propensity scores, statins (hazard ratio [HR] 0.46, 95% CI 0.36-0.58), beta blockers (HR 0.68, 95% CI 0.58-0.80), aspirin (HR 0.72, 95% CI 0.61-0.84), and ACE inhibitors (HR 0.80, 95% CI 0.69-0.94) were significantly associated with a reduced risk of long-term mortality in this cohort. The benefits of these therapies appear additive, and these data support the universal nature of atherosclerotic vascular disease, whether in the form of PAD or elsewhere.

Dyslipidemia

Several cholesterol-lowering trials in patients with dyslipidemia and CAD and/or PAD have evaluated the effects of lipid lowering on PAD. Initial studies, performed before the availability of statins, showed either regression or less progression of femoral atherosclerosis with lipid-lowering therapy.[38–40] The Program on the Surgical Control of the Hyperlipidemias (POSCH) randomized men with previous MI and dyslipidemia to diet therapy or diet therapy plus surgical ileal bypass. At 5 years, those in the surgical group had better control of lipid levels, decreased overall mortality, and decreased mortality from atherosclerotic coronary heart disease.[41]

Studies in the statin era confirm these initial results. For example, in the Heart Protection Study, which randomized 20,536 high-risk participants to 40 mg/day of simvastatin or placebo, a 24% relative risk reduction was observed in first-time cardiovascular events in the patients who received simvastatin. The subgroup of patients with PAD had similar cardiovascular benefits regardless of history of myocardial infarction (MI) or CAD. Even the subgroup population who had low-density lipoprotein cholesterol (LDL-C) levels less than 100 mg/dL at baseline benefited from statin therapy.[42] A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S), which included 4444 patients with angina or previous MI and a baseline total cholesterol level of 212 to 309 mg/dL, found that treatment with 20 to 40 mg of simvastatin per day reduced the incidence of new or worsening claudication by 38% (2.3% versus 3.6% with placebo).[43]

Independent of cholesterol-lowering effects, statin use improves pain-free walking distance and walking speed in patients with PAD and claudication.[44] Two studies randomized patients with claudication to simvastatin 40 mg daily or placebo. Aronow and colleagues reported an improvement in pain-free walking distance of 24% increase at 6 months and of 42% increase at 1 year after initiation of treatment. It is interesting to note that total walking distance and ABI did not improve.[45] In contrast, Mondillo and colleagues reported increases in ABI, total walking distance, and pain-free survival in patients randomized to simvastatin (**Fig. 27-5**).[46] Mohler and colleagues randomized 354 patients with claudication to atorvastatin 10 mg or 80 mg or placebo.[47] Patients receiving atorvastatin had an increased pain-free walking distance, but not total walking distance or ABI. Patients with PAD who take statins have been shown to have less annual decline in lower-extremity performance than those that do not.[48] Overall, the aggregate data suggest that statin use may increase the walking distance until the onset of pain, but statin use does not clearly affect total walking time or change lower-extremity blood flow as measured by ABI.

The current recommendations advocate a goal LDL-C of less than 100 mg/dL for patients with PAD; for very high-risk patients, the goal is an LDL-C below 70 mg/dL. All patients

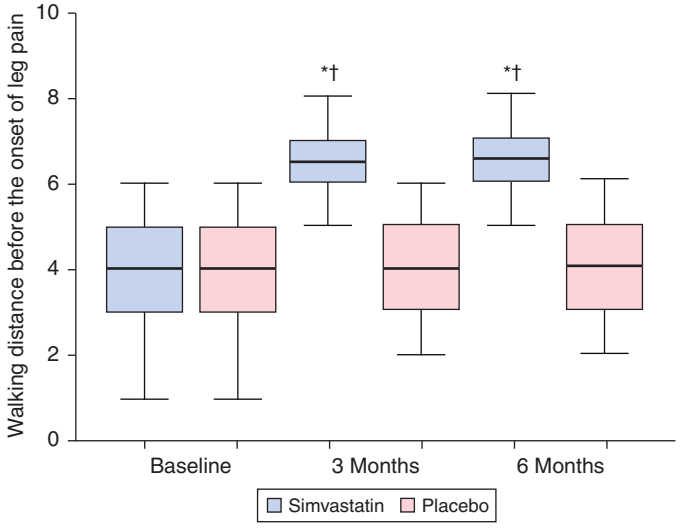


FIGURE 27-5 **Simvastatin can improve walking distance in patients with PAD.**[46] *(Modified from Mondillo S, Ballo P, Barbati R, et al: Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease,* Am J Med *114:359-364, 2003.)*



with PAD should be treated with statins as first-line lipid-lowering therapy, if tolerable.[24,35]

There is also a role for fibrate therapy in the treatment of PAD. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 patients aged 50 to 75 years with type 2 diabetes to either fenofibrate 200 mg/day or placebo for 5 years' duration. The risks of first amputation (45 versus 70 events; HR 0.64, 95% CI 0.44-0.94; $P=.02$) and minor amputation events without known large-vessel disease (18 versus 34 events; 0.53, 0.30-0.94; $P=0.027$) were lower for patients assigned to fenofibrate than for patients assigned to placebo, with no difference between groups in risk of major amputations.[49] A reduction in amputation events has not been similarly shown with statin therapy.

Smoking Cessation

Several nonrandomized studies have shown that patients who successfully quit smoking have decreased rates of PAD progression, critical limb ischemia, amputation, MI, and stroke, and have increased survival.[50,51] Unfortunately, the spontaneous cessation rates without intervention range from 2% to 5% in the United States, despite nearly 75% of smokers expressing a desire to stop. Given the importance of smoking cessation, it is important for health care providers to consistently convey to patients that discontinuation of tobacco products is extremely important to overall survival, well-being, and limb preservation.[52,53] Behavioral interventions can improve cessation rates, but only modestly. Only 5% of patients who receive physician advice, follow-up correspondence, phone calls, and supplementary visits will quit smoking.[54] Randomized trial evidence, however, has demonstrated that a 10-week intervention that results in just a 21.7% smoking cessation rate at 5 years significantly improves survival in patients with chronic lung disease compared with those treated with usual care.[55] Thus, efforts at cessation should be made.

Hennrikus and colleagues have specifically demonstrated that individuals with PAD respond to intensive counseling and education in a randomized trial of 124 patients. These researchers compared an intensive tobacco cessation counseling program with a minimal educational program over 6 months. Study participants assigned to the intensive intervention group were significantly more likely to be abstinent from tobacco at 6-month follow-up: 21.3% versus 6.8% in the minimal intervention group ($P=0.023$).[56]

Smoking cessation can be aided in many ways, including the use of pharmacotherapy such as short-term nicotine replacement products including gums, long-acting nicotine replacement patches, bupropion, or varenicline. Pharmacologic interventions are more effective than medical advice alone. In controlled studies, the rates of stopping smoking with use of pharmacologic treatment interventions has varied from 17% to 48% at 6 months and from 11% to 34% at 1 year.[57] Bupropion, via a poorly understood mechanism, diminishes the desire for smoking. It is associated with cessation rates of 27% to 35% at 6 months and 23% to 30% at 1 year.[58] Varenicline, a partial agonist selective for the $alpha_4$, $beta_2$ nicotinic acetylcholine receptor, is a newer agent than bupropion. Two large, randomized trials have suggested that varenicline performs better when the two are compared directly. In a study of 1025 smokers where patients were randomized to placebo, sustained-release bupropion, or varenicline, abstinence rates from weeks 9 to 52 were significantly elevated in the two drug arms compared with placebo. Cessation rates were 8.4%, 16.1%, and 21.9% respectively for individuals taking placebo, bupropion, and varenicline.[59] In a second large randomized trial, Jorenby and colleagues found similar abstinence rates in individuals treated with placebo, bupropion, or varenicline.[60]

The U.S. Public Health Service task force smoking cessation guidelines do not recommend any one of the first-line agents over another.[61] Instead, they recommend that patient preference and previous experience with the medications guide the choice of the first-line therapy (nicotine replacement, bupropion, and varenicline). Meta-analyses done for the guideline update addressed the question of whether any drug was more effective than the nicotine patch. In this analysis, there was no statistically significant difference between the patch and other nicotine replacement products or bupropion, but varenicline had a higher efficacy than the nicotine patch (OR 1.6, 95% CI 1.3-2.0). The analysis also compared the nicotine patch with combinations of drugs. The combination of nicotine patch and short-acting nicotine replacement products, used for an extended period of time, was more effective than the patch alone (OR 1.9, 95% CI 1.3-2.7), as was the combination of nicotine patch and sustained-release bupropion (OR 1.3, 95% CI 1.0-1.8).

Until further trials have been performed, varenicline and the combination of long-acting patch plus short-acting nicotine replacement therapies appear to be roughly equivalent first-line choices. Patients treated with varenicline should be monitored for possible adverse neuropsychiatric events.

Despite multiple options for the approach to tobacco cessation in individuals with PAD, there appears to be continued risk in individuals who successfully become abstinent. Data from the Women's Health Study demonstrate that although smoking cessation substantially reduces risk for PAD events in women, there remains an increased occurrence of PAD events in former smokers compared with individuals who never smoked.[62]

Hypertension

In a large number of clinical trials involving thousands of patients, antihypertensive drug therapy has been associated with a 35% to 40% mean reduction in the rate of stroke, a 20% to 25% reduction in MI, more than a 50% reduction in heart failure, and a significant reduction in the development of chronic kidney disease.[63] Although treatment of hypertension has been studied in many contexts, there are limited data available to determine whether treatment of hypertension will prevent the development of claudication or alter the course of PAD itself.

The Treatment of Mild Hypertension Study (TOMHS) showed that drug treatment in addition to nutritional interventions was superior to nutritional interventions alone in preventing the development of intermittent claudication and PAD over an average follow-up of 4.4 years.[64] Reports on the effect of blood pressure lowering on the ability to walk in patients with intermittent claudication are mixed.[65–67] However, these small studies have demonstrated that the ACE inhibitor captopril maintains and may increase walking distance in patients with claudication. Alpha-adrenergic blockers, beta blockers, and calcium channel blockers may adversely affect walking distance, particularly if there is a substantial decrease in systolic blood pressure. In a 6-month crossover trial of 20 hypertensive patients with PAD randomized to atenolol, labetalol, pindolol, captopril, or placebo, only individuals treated with captopril maintained walking distance.[67] This appears to be a class effect, as enalapril

and ramipril also seem to improve lower-extremity blood flow in patients with claudication.[68,69]

Antihypertensive therapy should be administered to hypertensive patients with PAD to achieve a goal of less than 140/80 mm Hg to reduce the risk of MI, stroke, heart failure, and cardiovascular death.[69a,69b]

In PAD patients with diabetes, the Appropriate Blood Pressure Control in Diabetes (ABCD) study supports intensive management of hypertension.[70] The ABCD study randomized 480 normotensive patients (baseline diastolic blood pressure of 80 to 89 mm Hg) with type 2 diabetes to either an intensive blood pressure regimen with enalapril or nisoldipine or placebo. Individuals were followed for 5 years. Fifty-three of the patients had PAD as defined by an ABI below 0.90. In patients with PAD, there were 3 cardiovascular events (13.6%) in the intensive treatment group compared with 12 events (38.7%) in patients taking placebo ($P = .046$). After adjustment for multiple cardiovascular risk factors, an inverse relationship between ABI and cardiovascular events was observed with placebo ($P = .009$), but not with intensive treatment ($P = .91$). Thus, with intensive blood pressure control, the risk of an event was not increased, even at the lowest ABI values, and was the same as in patients without PAD. The conclusion from the trial was that intensive blood pressure lowering to a mean of 128/75 mm Hg resulted in a marked reduction in cardiovascular events.

Diabetes Mellitus

To date, no prospective trials have been performed to assess whether improved glycemic control decreases the cardiovascular risk associated with PAD, the walking distance of patients with claudication, or the frequency of amputation. In a retrospective review of the Diabetes Control and Complications Trial of patients with type 1 diabetes mellitus, there was a 22% risk reduction in the development of PAD in the group that received intensive insulin therapy.[79] Epidemiologic studies also support the benefit of tight glycemic control. The prospective Belfast Diet Study of type 2 diabetic patients demonstrated an increasing risk for MI of 1.04 per mmol increase in fasting plasma glucose.[80] In the UK Prospective Diabetes Study of 2693 patients followed for nearly 8 years, patients in the highest tertile of HbA1c had a 1.5-fold greater risk for MI compared with those in the lowest tertile.[81] Although no prospective trial has demonstrated the noncoronary vascular benefits of improved glycemic control, it is nevertheless recommended. The current recommendations based on a joint position statement from the ADA and the European Association for the Study of Diabetes (EASD) advocate a less algorithm-driven treatment plan based on individualized comorbidities than previously articulated, but do not advocate a specific HbA1c goal for treatment.[82] However, the current position document does not specifically mention PAD at all. Previous versions of ADA guidelines recommended that all patients with diabetes and PAD should be aggressively treated to reduce their HbA1c levels to less than 7%.[83]

Further reductions in goal HbA1c levels have been tested in several recent trials.[84–86] Although intensive glycemic control reduced the incidence of microvascular events, there were no significant reductions in macrovascular outcomes between standard and intensive glycemic control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, for example, randomized 10,251 patients with a history of a cardiovascular event or significant cardiovascular risk to intensive glycemic control (target HbA1c below 6.0%) or standard glycemic control (target HbA1c 7.0% to 7.9%). Within 12 months of randomization, the intensive glycemic group reached a median HbA1c of 6.4% (from a baseline median of 8.1%) compared with a median HbA1c of 7.5% in the standard glycemic group. However, the glycemic control arm was stopped because of an increased mortality rate in the intensive glycemic control group.[84] At this time, the optimal HbA1c goal for individuals with PAD has not been clearly defined for all patients.

Despite a paucity of clinical trial evidence, meticulous foot care is also recommended for patients with diabetes and PAD to reduce the risk of skin ulceration, necrosis, and subsequent amputation. This includes the use of appropriate footwear to avoid pressure injury, daily inspection and cleansing by the patient, and the use of moisturizing cream to prevent dryness and fissuring. Frequent foot inspection by patients and health care providers is thought to enable early identification of foot lesions and ulcerations and facilitate prompt referral for treatment.[83]

Obesity and Weight Reduction

An association between obesity and PAD has been observed in some studies but not others. For example, in the Framingham cohort of 5209 patients, relative weight was only a weak risk factor for claudication.[7] In contrast, obesity, as determined by a body mass index over 30, was not a risk factor for PAD or intermittent claudication in the Edinburgh Artery Study, Whitehall study, or Lipid Research Clinics study.[87–89] Despite the mixed evidence for a direct relationship between obesity and PAD, obesity may heighten the risk for PAD by increasing the prevalence of other previously established risk factors. For example, in a study of 8688 men followed for 5 years, being overweight was the most significant predictor of who was going to develop type 2 diabetes mellitus.[90] McDermott and colleagues have shown that over 4 years of follow-up, patients with intermittent claudication and a body mass index over 30 kg/m^2 had significantly more functional decline.[91] Thus it stands to reason that any decrease in weight will decrease the work required for walking and will improve exercise capacity. Therefore, weight reduction is recommended for patients with PAD.

Antiplatelet Therapy

There is substantial evidence that the cardiovascular morbidity and mortality related to PAD in patients with diabetes is related to platelet activity and inflammation. Platelet activity can be modified by the use of antiplatelet agents. The data supporting the use of antiplatelet agents for the prevention of cardiovascular events in patients with PAD in general is mixed, as is described here.

A meta-analysis of approximately 150 prospective controlled trials of antiplatelet therapy (mostly aspirin) has been reported as part of the Antithrombotic Trialists' Collaborative. This analysis combined data from more than 135,000 individuals with evidence of cardiovascular disease, including PAD. Investigators demonstrated a 22% reduction in the odds ratio in the composite primary endpoint of MI, stroke, and vascular death in patients taking antiplatelet therapy compared with controls. When the subset of approximately 9000 patients with claudication was analyzed, the protective effect of antiplatelet therapy was similar.[92] A more recent meta-analysis of 18 prospective trials totaling 5269 patients with PAD found that aspirin therapy compared with



placebo was not associated with significant reductions in all-cause or cardiovascular mortality, MI, or major bleeding.[93]

The Aspirin for Asymptomatic Atherosclerosis (AAA) trial enrolled asymptomatic patients with ABI of 0.95 or lower (instead of the standard cutoff value of 0.90 used in the multisociety guidelines) to 100 mg of aspirin daily or placebo. After a mean 8.2-year follow-up there were no differences in the composite number of vascular events, defined as MI, stroke, or coronary revascularization, between groups treated with aspirin or placebo.[94]

Specifically with regard to diabetic patients and PAD, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD), trial enrolled diabetic patients with asymptomatic PAD. This study did not find a beneficial effect of aspirin compared with placebo on a primary endpoint of death from coronary disease, nonfatal MI, nonfatal stroke, or amputation.[95]

Clopidogrel has also been studied in patients with PAD. The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared aspirin versus clopidogrel in patients with recent stroke, recent MI, or established PAD.[96] Patients treated with clopidogrel had an 8.7% relative risk reduction (5.3% versus 5.8%, $P = .043$) in the primary endpoint of stroke, MI, or vascular death compared with those treated with aspirin. In the subset analysis of patients with PAD who were enrolled in the trial, there was a 23.8% relative risk reduction in favor of clopidogrel. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial compared the efficacy of dual antiplatelet therapy with clopidogrel plus aspirin versus aspirin alone in patients with established CAD, cerebrovascular disease, or PAD, as well as in patients with multiple atherosclerotic risk factors.[97] Overall, dual antiplatelet therapy produced no significant benefit compared with aspirin alone on the primary endpoint of MI, stroke, or cardiovascular death. Among the 3096 patients with PAD who enrolled, clopidogrel plus aspirin did reduce the rates of MI and hospitalization for ischemic events compared with aspirin alone.[98]

Oral anticoagulation with warfarin has also been studied in patients with PAD. The Warfarin Antiplatelet Vascular Evaluation (WAVE) study evaluated antiplatelet therapy in addition to warfarin compared with antiplatelet therapy alone in patients with PAD.[99] There was no significant improvement with warfarin therapy; however, patients treated with warfarin and antiplatelet agent together had more life-threatening bleeding than those treated with warfarin alone.

Current guidelines recommend that patients with PAD be treated with an antiplatelet drug, such as aspirin or clopidogrel (recommended as a class I recommendation for symptomatic patients and a class II recommendation for asymptomatic patients) to reduce the risk of MI, stroke, or vascular death.[24] Oral anticoagulants are not recommended to reduce cardiovascular events. Newer antiplatelet agents (such as prasugrel or ticagrelor) and nonwarfarin anticoagulants (such as factor Xa inhibitors or direct thrombin inhibitors) have not been rigorously studied in patients with PAD for the prevention of cardiovascular events.

Renin Angiotensin System Antagonism in Peripheral Artery Disease

Although the achievement of goal blood pressure level outweighs the use of a specific class of antihypertensive agents, renin-angiotensin system antagonists should be considered an initial drug class of choice.

Both ACE inhibitors and ARBs have favorable effects on the cardiovascular system beyond their ability to lower blood pressure. Based on the Heart Outcomes Prevention Evaluation (HOPE) study, patients with diabetes or evidence of vascular disease plus one other cardiovascular risk factor who received ramipril had a 22% relative risk reduction of the combined endpoint of stroke, MI, and death compared with patients who received placebo, despite a baseline blood pressure considered at goal for most patients. These outcomes were seen despite a modest overall blood pressure reduction of 3/2 mm Hg.[71] Overall, 17.8% of patients in the placebo group reached the primary study endpoint of MI, stroke, or cardiovascular death. The rate was 22% for the 4051 patients with PAD compared with 14.3% for the 5246 patients without PAD.

In the European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA), 12,218 patients with stable CAD were randomly assigned to perindopril or placebo. After a mean follow-up of 4.2 years, cardiovascular events were significantly decreased in patients treated with perindopril. All predefined subgroups, including the 883 patients who had documented PAD, benefited from perindopril.[72] These data concurred with the findings of the HOPE trial. Thus, based on two studies of patients with normal blood pressure at rest and only modest changes in blood pressure with therapy, ACE inhibitors decrease cardiovascular morbidity and mortality more than expected with the observed blood pressure lowering.

Similar to ACE inhibitors, ARBs have documented cardiovascular benefits beyond their antihypertensive properties. In particular, ARBs have been shown to improve endothelial function through decreased vascular inflammation.[73] Patients with high cardiovascular risk, including those with PAD, are likely to benefit from ARBs. ARBs, such as losartan and candesartan, have shown morbidity and mortality benefits either alone or in combination with ACE inhibitors, as demonstrated in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) studies.[74,75] In the LIFE study, losartan was compared with atenolol in hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy. Overall, losartan significantly lowered the incidence of cardiovascular events, particularly stroke, despite similar decreases in blood pressure. Thus, similar to ACE inhibitors, ARBs should be thought of as having cardiovascular benefits beyond blood pressure reduction. It is interesting to note that in Swedish National Registry data, patients treated with candesartan were less likely to develop PAD compared with patients treated with losartan despite similar blood pressure lowering.[76]

Beta-adrenergic Blockers in Peripheral Artery Disease

The commonly held belief that beta-blocking agents worsen claudication and shorten the amount of exercise required to bring on discomfort in the legs has been well challenged. In a carefully performed meta-analysis of 11 randomized, controlled trials, Radack and Deck demonstrated that beta-adrenergic blocker therapy does not worsen claudication symptoms in people with PAD.[77] Only 1 of 11 studies in this meta-analysis showed that pain-free and maximal treadmill walking distances were decreased by atenolol, labetalol, or pindolol, but not captopril. However, beta blockers should not be considered as first-line agents in the treatment

of hypertension and PAD, given the beneficial effects of ACE inhibitors and ARBs already discussed. If there are clear indications for beta-blocker use, such as congestive heart failure, post-MI status, angina pectoris, or arrhythmias or for perioperative cardiovascular protection, then beta blockers can and should be used.[78]

Therapy for the Treatment of Claudication

In addition to modifying risk factors to improve overall cardiovascular morbidity and mortality, there are noninterventional strategies available to treat the mobility limitations caused by symptomatic PAD. Only two medications carry U.S. Food and Drug Administration (FDA) approval for the improvement of walking distance in PAD: pentoxifylline and cilostazol.

Pentoxifylline

Pentoxifylline is a rheologic modifier approved by the FDA for symptomatic relief of claudication. It is thought to act by improving red blood cell and leukocyte flexibility, inhibiting neutrophil activation and adhesion, decreasing fibrinogen concentrations, and reducing blood viscosity, permitting improved muscular perfusion. Studies investigating the efficacy of pentoxifylline have yielded conflicting results. A meta-analysis found that pentoxifylline improved walking distance by 29 meters compared with placebo.[100] The improvement was approximately 50% in the placebo group, whereas pentoxifylline added an additional 30%. The benefit was substantially less, however, than that achieved with a supervised exercise program.[101]

The beneficial response to pentoxifylline is small in most patients, and the overall data are insufficient to support its widespread use in patients with claudication. Pentoxifylline may be considered for patients who cannot take cilostazol, have not responded adequately to an exercise program, and/or are not candidates for revascularization, either with percutaneous or surgical approaches.

Cilostazol

Cilostazol is a phosphodiesterase-3 inhibitor that suppresses platelet aggregation and is a direct arterial dilator.[102] The efficacy of cilostazol has been demonstrated in several studies[103–105] and in a meta-analysis[106] of eight randomized, placebo-controlled trials that included 2702 patients with stable moderate-to-severe claudication. In the meta-analysis, treatment with 100 mg twice daily for 12 to 24 weeks increased maximal and pain-free walking distances by 50% and 67%, respectively. Because cilostazol is a phosphodiesterase inhibitor similar to milrinone, it is contraindicated in patients with symptomatic congestive heart failure or patients with a left ventricular ejection fraction less than 40%.

Cilostazol is more effective than pentoxifylline when compared directly. Superiority was illustrated in a trial of 698 patients randomized to cilostazol, pentoxifylline, or placebo for 24 weeks. The increase in mean walking distance over baseline with pentoxifylline and placebo was the same (30% and 34%, respectively), but the increase with cilostazol was significantly greater (54%) (**Fig. 27-6**).[107] The most common adverse effects with cilostazol are headache, palpitations, and diarrhea. The optimal dose of cilostazol is 100 mg twice daily. The medication should be given on an empty stomach. Because of the inhibitory effects of cilostazol on drug metabolism, the dose should be halved in patients taking medications that inhibit the cytochrome P-450 isoenzymes CYP3A4 and CYP2C19 (e.g., erythromycin, diltiazem, omeprazole).[108]

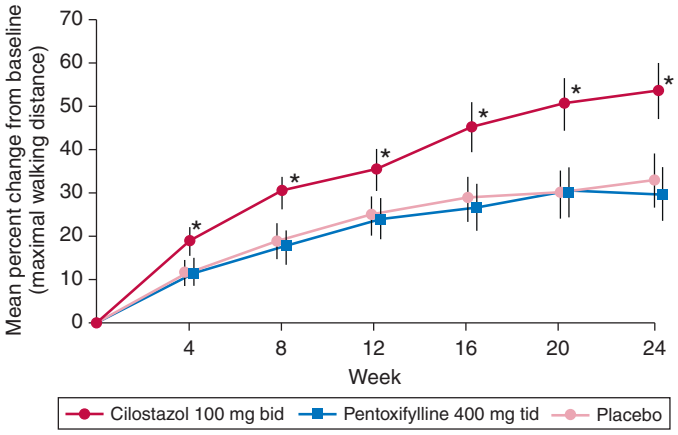


FIGURE 27-6 Cilostazol versus pentoxifylline for the treatment of claudication.[107] *(Modified from Dawson DL, Cutler BS, Hiatt WR, et al: A comparison of cilostazol and pentoxifylline for treating intermittent claudication,* Am J Med *109:523-530, 2000.)*

Other Pharmacologic Agents

Multiple other agents have been used in the treatment of claudication. Naftidrofuryl, a 5-hydroxytryptamine serotonin receptor inhibitor, has been available in Europe for a number of years. The mechanism of action of this drug is not clear, but it is thought to promote glucose uptake and increase adenosine triphosphate levels. A meta-analysis of four trials showed an increase in the time to initial pain development with treadmill walking over a 3- to 6-month period.[109]

Buflomedil is an alpha-adrenolytic agent available in Europe, but not the United States, that has been used in the treatment of claudication. The Limbs International Medicinal Buflomedil (LIMB) trial evaluated the efficacy and safety of buflomedil in 2078 patients with claudication and an ABI of 0.3 to 0.8, in a randomized, placebo-controlled trial. At a median follow-up of 2.8 years, the rate of a composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, symptomatic deterioration in PAD, or leg amputation was significantly lower in the patients who received buflomedil (9.1% versus 12.4%). The benefit was largely driven by a reduction in symptoms of PAD.[110]

Ginkgo biloba has also been studied in the treatment of claudication with some modest success. Ginkgo is thought to act via an antioxidant mechanism that inhibits vascular injury. It is also thought to have some antithrombotic effects. The effect of ginkgo has been reviewed in a meta-analysis that showed that patients receiving ginkgo extract increased pain-free walking by approximately 34 meters, a significant increase compared with placebo.[111]

Many other agents have been tried in the treatment of symptomatic claudication. These include estrogen replacement therapy, chelation therapy with intravenous ethylenediaminetetraacetic acid (EDTA), and vitamin E supplementation. None have been shown to have significant benefit, and none are recommended by current therapy guidelines.

Exercise

Many prospective trials have demonstrated that supervised exercise is an effective method of treating patients with claudication.[112] The magnitude of the effect from a supervised exercise program exceeds that achieved with any of the

TABLE 27-2 Effect of Supervised Exercise from a Meta-analysis of 21 Studies

COMPONENTS OF EXERCISE PROGRAMS	NO. OF STUDIES	CHANGE IN THE DISTANCE TO ONSET OF PAIN, m	P	CHANGE IN THE DISTANCE TO MAXIMAL PAIN, m	P
Exercise Duration					
≤30 min/session	8	143.1 ± 162.8	.039	143.6 ± 418.9	.007
>30 min/session	6	314.2 ± 172.4		652.6 ± 363.9	
Exercise Frequency					
<3 sessions/wk	7	177.8 ± 129.6	.048	249.0 ± 349.5	.045
≥3 sessions/wk	11	270.7 ± 221.4		541.5 ± 253.2	
Length of Program					
<26 wk	10	131.9 ± 158.6	.008	275.1 ± 228.3	.009
≥26 wk	11	345.6 ± 161.7		518.5 ± 409.2	
Claudication Pain End Point Used During Training Sessions					
Onset of pain	15	104.7 ± 91.2	.007	195.5 ± 78.3	.005
Near-maximal pain	6	350.2 ± 246.2		606.8 ± 426.6	
Mode of Exercise					
Walking	6	294.3 ± 289.7	.042	511.9 ± 483.2	.023
Combination of exercises	15	152.1 ± 158.4		286.9 ± 127.4	
Level of Supervision					
Supervised	11	238.3 ± 120.5	.476	448.6 ± 291.7	.518
Combination of home and supervised	8	208.4 ± 198.4		339.8 ± 471.9	

Values for each componant are adjusted means ± standard deviations (SDs) of the change in the distances to onset and to maximal claudication pain after the other five exercise program components were controlled for.

Data from Gardner AW, Poehlman ET: Exercise rehabilitation programs for the treatment of claudication pain, A meta-analysis, *JAMA* 274:975-980, 1995.

pharmacologic agents available. A meta-analysis of 21 studies by Gardner and Poehlman,[113] which included both randomized and nonrandomized trials, showed that pain-free walking time improved by an average of 180% and maximal walking time by 120% in patients with claudication who underwent supervised exercise training (**Table 27-2**). Furthermore, a meta-analysis from the Cochrane Collaboration that included only randomized, controlled trials showed that exercise improved maximal walking ability by an average of 150% (range 74% to 230%).[114] The most recent randomized, controlled trial of exercise in PAD was the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study.[115] Investigators randomized 111 patients with aortoiliac disease to medical therapy, medical therapy plus supervised exercise, or medical therapy plus endovascular revascularization. Patients in the medical therapy plus supervised exercise therapy group were able to increase their peak walking time by 5.8 ± 4.9 minutes compared with 1.2 ± 2.6 minutes for those in the medical therapy alone group. It is interesting to note that the increase in peak walking time was intermediate in the revascularization group, but quality of life as measured by the Peripheral Artery Questionnaire improved most in the revascularization group.

There are several mechanisms by which exercise training may improve claudication, although the available data are not sufficient to render firm conclusions regarding their relative importance. These mechanisms include improved endothelial function via increases in nitric oxide synthase and prostacyclin; reduction of local inflammation; increased exercise pain tolerance; induction of vascular angiogenesis; improved muscle metabolism by favorable effects on muscle carnitine metabolism; and reductions in blood viscosity and red cell aggregation.[116]

Although less well studied, exercise may also improve survival in PAD. This idea was addressed in a prospective, observational study of 225 men with PAD in whom physical activity was measured with a vertical accelerometer. Patients were followed for a mean duration of 57 months, over which time 33% of patients died. Individuals in the highest quartile of accelerometer-measured activity had a significantly lower mortality than those in the lowest quartile (HR 0.29, 95% CI 0.10-0.83).[117]

The current PAD guidelines state that a program of supervised exercise training is recommended as an initial treatment modality for patients with claudication (class I, level of evidence A) and that supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times per week for a minimum of 12 weeks (class I, level of evidence A).[24,35]

Exercise programs have several important limitations. First patients must be motivated, which is often difficult when they experience claudication-related pain whenever they walk. Second, the best results occur when patients enroll in a supervised program as with cardiac rehabilitation, ensuring compliance. Unfortunately, there is often a lack of financial reimbursement for supervised programs, and patients instructed by health care providers to exercise on their own do not achieve the same improvement as those in structured programs.[118]

REVASCULARIZATION

Many patients do not experience optimal improvement in symptoms related to PAD from medical therapy or risk factor modification alone. Two general revascularization strategies exist: endovascular interventions and open surgical techniques. As in the coronary circulation, the success of

revascularization in the lower extremities depends on many variables including lesion location, lesion length, and the nature of the distal runoff. Diabetes alters the distribution of lower-extremity atherosclerosis so that these patients tend to have severe arterial occlusive disease below the knee in the runoff vessels. As the distal runoff declines, the results of endovascular interventions worsen and the need for surgery increases.

Endovascular Management

In general, endovascular revascularization is more appropriate in patients with relatively focal disease in arteries above the knee.[119] However, short-term success rates for opening long totally occluded vessels and below-the-knee arteries are improving.[120] Thus far, the best results have been seen in aortoiliac vessels, in which 1-year patency rates of 80% to 90% have been demonstrated.[36,121,122] Femoral interventions have 1-year patency rates that vary widely, from approximately 30% to 80%, with diabetes adversely affecting the long-term rates of success.[123–125] However, in diabetic patients with reasonable runoff, patency rates are similar to those in nondiabetics.[126]

Surgical Management

In diabetes, open surgical revascularization tends to have greater durability than endovascular procedures. Bypass to the tibial or pedal vessels with autogenous vein is the most predictable method of improving blood flow to the threatened limb. Surgical bypass with greater saphenous vein is the procedure of choice for patients with diabetes and tibial disease; however, this comes at the price of increased periprocedural cardiovascular morbidity and mortality.[6] The specific operation must take into account the anatomic location of the arterial lesions and the presence of comorbid conditions. The surgical procedure is planned after identification of the arterial obstruction by imaging, ensuring that there is sufficient arterial inflow to and outflow from the graft to maintain patency.

Revascularization is the definitive therapy for the management of patients with chronic limb ischemia, with the aim of healing ischemic ulcers and preventing limb loss. Although most limbs can be revascularized, the lack of target vessel, the unavailability of autogenous vein, or irreversible gangrene means that some cannot. In these patients, amputation is often a better option than prolonged, but failing, medical therapy.

APPROACH TO THE TREATMENT OF DIABETIC PATIENTS WITH PERIPHERAL ARTERY DISEASE

Overall, the approach to treatment of the diabetic patient with PAD is similar to that of other patients with PAD. A schematic of the overall approach is presented in **Figure 27-7**.

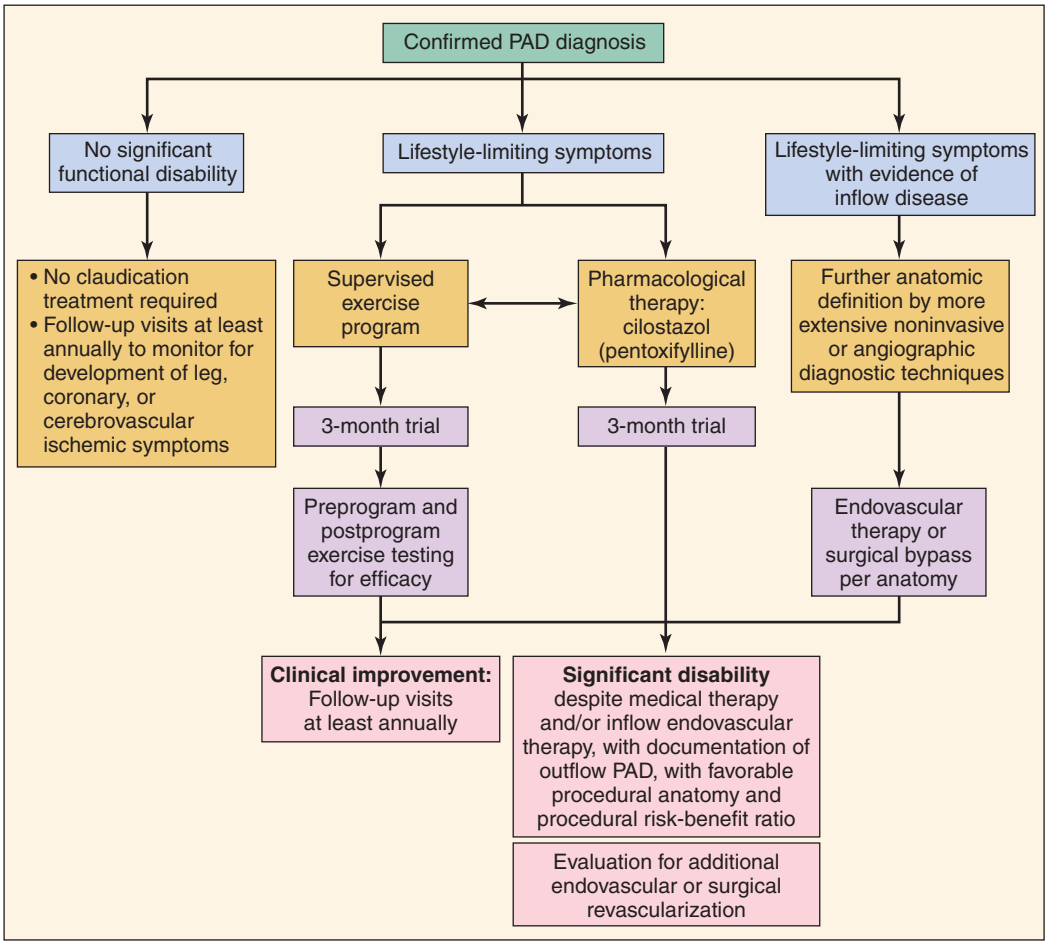


FIGURE 27-7 Treatment algorithm for peripheral artery disease. *(Modified from multi-society guidelines, from Creager and Libby in Braunwald's Heart Disease, Figure 61-17, page 1352).*

SUMMARY AND CONCLUSION

PAD is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in nondiabetic individuals. Moreover, the presence of PAD is an important and potent marker of overall cardiovascular risk. Because the major threat to patients with diabetes and PAD is from cardiovascular events (and not limb-related events), the primary therapeutic goal is to modify atherosclerotic risk factors. Risk factor management includes lifestyle modifications, treatment of associated conditions (tobacco cessation, hypertension, dyslipidemia, diabetes itself), and prevention of ischemic events with antiplatelet therapy. A supervised exercise program, tobacco cessation, and/or cilostazol are the preferred first steps in the management of symptomatic PAD. Revascularization plays an important role in the management of patients for whom risk factor modification and pharmacologic therapy have proven inadequate.

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28 Cerebrovascular Disease in Patients with Diabetes



Frank Joachim Erbguth

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Stroke—in particular the ischemic subtype—is one of the major vascular manifestations of diabetes, together with coronary heart disease (CHD), peripheral arterial occlusive disease, and diabetic retinopathy. The relationship between hyperglycemia and stroke is bidirectional: on the one hand, diabetic patients exhibit more than a twofold risk of ischemic stroke compared with patients without diabetes (see the later discussion of epidemiology of stroke in diabetes), even after statistical correction for other vascular risk factors. On the other hand, acute stroke can generate acute disturbances of glucose metabolism with poststroke hyperglycemia (PSH) (see the later discussion of PSH), which is associated with an approximate twofold risk of a bad outcome. Treatment of hyperglycemia in patients with diabetes combined with multiple vascular risk factor management can substantially decrease the rate of stroke in primary as well as in secondary prevention. However, diabetes-associated end-organ damage to the brain is not only restricted to neuronal damage by strokes, but also involves chronic and insidious damage of the brain resulting in cognitive decline and dementia. Dementia in patients with diabetes not only results from vascular-mediated neuronal damage manifesting as vascular dementia (VD), but also is caused by an enhancement of neurodegenerative changes in the brain manifesting as Alzheimer disease (AD). In addition, between diabetes and dementia, bidirectional relations are likely: on the one hand, people with diabetes have double the risk of developing dementia by mechanisms that are not yet fully understood; and on the other hand, the cognitive and behavioral manifestations of dementia such as lack of physical exercise and interference with therapeutic compliance may lead to disturbances of glucose metabolism resulting in lability of glucose control, including an increased frequency of episodes of severe hypoglycemia.

EPIDEMIOLOGY OF STROKE IN DIABETES

Epidemiology of Stroke: General Observations and Time Trends

Stroke is the second most frequent cause of death worldwide and the second leading cause of long-term disability in industrialized countries. The incidence of stroke is considerable across the United States and European countries, with the subtypes of ischemic stroke and transient ischemic attack (TIA) being the most common events (80% to 85%). Stroke incidence in European epidemiologic studies ranges from 114 cases/100,000 persons per year in France for first-ever stroke to 350 cases/100,000 persons per year in Germany for all stroke subtypes. Stroke prevalence estimates range from 1.5% in Italy and 3% in the United Kingdom and United States.[1]

The epidemiologic Oxford Vascular Study[2] analyzed the frequency of three types of vascular events (acute coronary, cerebrovascular, and peripheral) in a population of 91,106 inhabitants in Oxfordshire, United Kingdom, from 2002 to 2005. Cerebrovascular events (618 strokes and 300 TIAs), with a proportion of 45%, were more frequent than coronary

vascular events, which affected 42% of the cohort (159 ST-segment elevation myocardial infarctions (STEMIs); 316 non–ST-elevation MIs; 218 unstable angina events; 163 sudden cardiac deaths), and peripheral vascular events, with an incidence of 9% (43 aortic; 53 embolic visceral or limb ischemic events; 92 critical limb ischemic events). Sixty-two deaths remained unclassifiable. The relative incidence of cerebrovascular events compared with coronary events was 1.19 (95% confidence interval [CI] 1.06-1.33) overall, and 1.40 (1.23-1.59) for nonfatal events. Event and incidence rates rose steeply with age in all arterial territories, with 735 (80%) cerebrovascular, 623 (73%) coronary, and 147 (78%) peripheral vascular events in 12,886 (14%) individuals aged 65 years or older; and 503 (54%), 402 (47%), and 105 (56%), respectively, in the 5919 (6%) aged 75 years or older (**Fig. 28-1**). Similar data were shown by French investigators.[3]

A comparison of incidence rates among different subtypes of stroke shows approximately 80% to 85% for ischemic stroke, 10% to 15% for intracerebral hemorrhage, and 5% for subarachnoid hemorrhage. It is not surprising that all studies have demonstrated that the incidence and prevalence of stroke in general increase with age.[1] However, the stroke subtype involving subarachnoid hemorrhage, because of its distinct cause (ruptured aneurysms), does not follow this pattern. The stroke incidence is higher in men than in women of the same age, based on age-adjusted data. Some studies on time trends of stroke epidemiology have indicated that the incidence and the individual personal risk have decreased during the last 20 years.[1]

Stroke mortality rates have been decreasing consistently over time, with recent reports indicating a 29.2% reduction in stroke mortality between 1999 and 2008 in the United States. A German registry found decreased mortality rates from 52.4 deaths per population of 100,000 in 2000 to 32.3 deaths per 100,000 in 2008 in both men and women combined; a greater rate of decline was observed in women.[1] Such increased survival of stroke patients may be linked to advances in preclinical and hospital treatment in acute stroke and in neurorehabilitation.

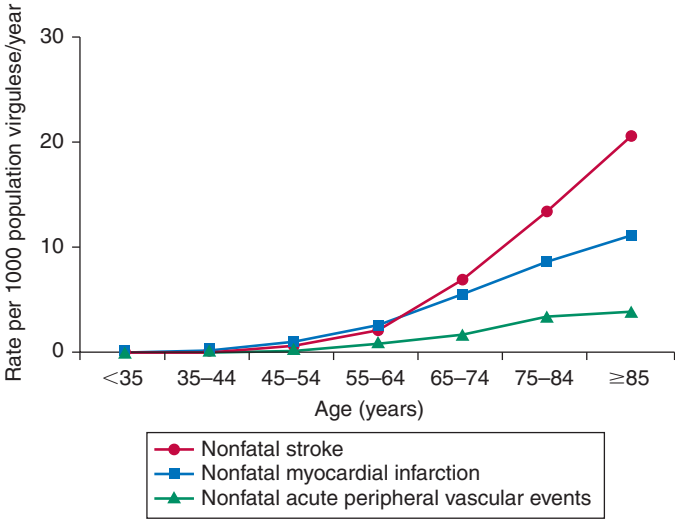


FIGURE 28-1 Age-specific event rates for nonfatal stroke (red line), nonfatal myocardial infarction (blue line), and nonfatal acute peripheral vascular events (green line). *(Modified from Rothwell PM, Coull AJ, Silver LE, et al: Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories [Oxford Vascular Study],* Lancet *366:1773-1783, 2005.)*

In the United Kingdom, an analysis of 32,151 stroke patients within the UK General Practice Research Database[4] revealed that stroke incidence fell significantly by 30% from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008. Fifty-six–day stroke mortality after first stroke was reduced significantly from 21% in 1999 to 12% in 2008. Stroke prevalence, however, increased significantly by 12.5%, from 6.40/1000 in 1999 to 7.20/1000 in 2008. The positive changes in stroke incidence coincided with a marked increase in primary care prescription of primary and secondary cardiovascular preventive medications such as lipid-lowering, antihypertensive, and antithrombotic drugs. Despite these positive findings, the study clearly demonstrated an underuse of oral anticoagulation in patients with atrial fibrillation (AF) at high risk of stroke, and lower use of all preventive treatments in women compared with men.

Diabetes and Other Risk Factors for Stroke

The risk of stroke associated with diabetes has been assessed predominantly in people with type 2 diabetes, because stroke is more common in that population than in the age group typical of persons with type 1 diabetes. Epidemiologic studies identified a twofold to fourfold increase in stroke risk for persons with diabetes.[5] As early as 1988, a population-based study demonstrated diabetes mellitus (DM) as an independent risk factor for stroke; during a follow-up of 3778 persons aged 50 to 79 years over 12 years, diabetes was associated with an increase in risk of 1.8 in men (95% CI 1.0-3.2) and 2.2 in women (95% CI 1.0-4.5).[6] The Nurses' Health Study observed 120,000 women for more than 8 years and found an unadjusted 5.4-fold increase in stroke risk that was associated with diabetes and, after correction for other confounding variables, an adjusted threefold increased stroke risk with diabetes.[7] During the longest observation period of 30 years in the Framingham Heart Study, a 2.5- to 3.6-fold increased risk of stroke in diabetic patients was found.[8] A meta-analysis of 102 prospective studies including 530,083 participants demonstrated a hazard ratio (HR) for ischemic stroke of 2.3 (95% CI 2.0-2.7) for patients with versus without diabetes.[9] A Finnish cohort study with 25,155 men and 26,423 women aged 25 to 74 years showed that diabetes at baseline carried a similar risk for stroke as a prior stroke (PS) at baseline.[10]

The duration of diabetes was independently associated with ischemic stroke risk according to data from the Northern Manhattan Study, adjusting for other risk factors. The observed risk increase associated with diabetes overall was 3% each year, and tripled with diabetes duration of 10 years or longer (**Table 28-1**).[11]

Assuming a population-wide prevalence of diabetes of 10%, these epidemiologic findings indicate a diabetes-attributable risk of stroke of approximately 12%. Hence, one in eight cases of stroke may be attributable to diabetes. Taking into account overall stroke mortality in general and its observed increased risk in diabetes, cerebrovascular disease causes approximately 20% of deaths of diabetic patients.[5]

Comparison of Vascular Risk Factors Between Stroke and Coronary Heart Disease

The case-control study INTERSTROKE[12]—analogous to the INTERHEART study—examined the worldwide burden of stroke and the quantitative impact of known risk factors in different countries, in particular in developing countries.

TABLE 28-1 Duration of Diabetes and Ischemic Stroke Risk

DIABETES DURATION (YEARS)	ADJUSTED HAZARD RATIO (HR)	95% CONFIDENCE INTERVAL (CI)
0-5	1.7	1.1-2.7
5-10	1.8	1.1-3.0
>10	3.2	2.4-4.5

Data from Banerjee C, Moon YP, Paik MC, et al: Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 43:1212-1217, 2012.

TABLE 28-2 Impact of Ten Vascular Risk Factors on Stroke and Myocardial Infarction: Odds Ratios and Percentage of the Population Attributable Risk (PAR)

RISK FACTOR/ BEHAVIOR	ODDS RATIO	PAR (%) FOR STROKE	PAR (%) FOR MYOCARDIAL INFARCTION
1. Arterial hypertension	2.64	34.6	17.9
2. Waist-to-hip ratio	1.65	26.5	20.1
3. Regular physical activity	0.69	28.5	12.2
4. Smoking	2.09	18.9	35,7
5. Diet risk score	1.35	18.8	13.7
6. Diabetes	1.36	5.0	9.9
7. Alcohol intake	1.51	3.8	6.7
8. Psychosocial factors (stress, depression)	1.3	9.8	32.5
9. Cardiac causes	2.38	6.7	—
10. Ratio of apolipoproteins B to A1	1.89	24.9	49.2

Of all fatal strokes worldwide, 85% occur in countries with low to middle income, and the number of strokes worldwide is massively driven by the increase in stroke incidence in developing and newly industrialized countries. Comparing 3000 stroke patients (78% ischemic stroke, 22% hemorrhagic stroke) and 3000 controls, the study extracted the 10 risk factors listed in decreasing order in **Table 28-2** (odds ratios [ORs] and percentage of the population attributable risk [PAR]). For comparison, the corresponding numbers from the INTERHEART study are given in a third column.

Collectively the listed 10 risk factors account for 90% of all strokes, and the first five risk factors—namely, arterial hypertension, smoking, abdominal adiposity, diet habits, and little physical exercise—explain 80% of all strokes. Hypertension was the most important individual epidemiologic risk factor, which tripled the stroke risk, and therefore has a higher relative importance for the risk of stroke than for the risk of CHD. DM as the sixth strongest by PAR% was placed in the middle field, being surrounded by diabetes-related risk factors such as adiposity, lack of physical exercise, and diet habits.

From the mentioned epidemiologic data, an individual stroke risk calculation can be deduced. Kothari and colleagues[13] developed a mathematical model from the United Kingdom Prospective Diabetes Study (UKPDS) data to calculate an individual's risk of stroke within the following 5 years. In this model, for example, a 67-year-old smoker with arterial hypertension, hypercholesterolemia, and diabetes duration of 12 years has a 10.5% risk of stroke within the next 5 years.

It is not surprising that diabetes not only doubles the risk for a first-ever stroke, but in the same manner doubles the risk for a recurrent stroke after a first event.[14,15]

Obviously, there has been a decline in cardiovascular death including stroke in individuals with diabetes; a recent report from the U.S. National Institutes of Health compared 3-year death rates between 1997 and 2004 and found a decline in the cardiovascular disease (CVD) death rate of 40%.[16]

Diabetes as a Stroke Risk Factor IN Younger Patients

Type 1 and type 2 diabetes play an important role as stroke risk factors, particularly in younger and middle-aged patients, because in these age groups other competing stroke risk factors are less prevalent and henceforth contribute less attributable risk than at older ages. According to an observational study in the United States of persons aged 18 to 44 years, diabetes raised the relative stroke risk from 6-fold to 23-fold, depending on gender and race or ethnicity.[17] In general, in patients younger than 60 years, the relative risk (RR) of stroke in those with versus without diabetes is approximately double that of individuals older than 70 years.[9] According to calculations from several studies, diabetes leads to an advanced cerebrovascular aging of approximately 10 to 15 years.

Multiplicative Risk Increase by Additional Vascular Risk Factors

Patients with diabetes almost always have additional vascular risk factors such as arterial hypertension, dyslipoproteinemia, obesity, lack of physical exercise, and nonvalvular AF. These comorbidities not only add to the risk of stroke from diabetes, but multiplicatively affect the risk of stroke. Some studies, for example, found that the combination of diabetes and hypertension was associated with a 5-fold to 10-fold increased risk of stroke, suggesting a synergistic impact on stroke risk.[18]

Stroke Risk in Prediabetes- and Diabetes-Associated Metabolic Risk Configurations (Insulin Resistance, Metabolic Syndrome, Adiposity)

Prediabetes (Impaired Fasting Glucose, Impaired Glucose Tolerance, Hemoglobin A1c)

Not only in diabetes per se, but also in prediabetic states, the risk for cerebrovascular disease is increased, although in general more modestly than with fully established diabetes. Prediabetes is defined as the condition in which glycemic variables are higher than normal but lower than the established diabetes thresholds. Prediabetes is a high-risk state for diabetes development: 5% to 10% of people with prediabetes will convert to diabetes each year.

A prospective study found a significant relationship between levels of fasting plasma glucose (FPG) even below the diabetes threshold and the incidence of stroke in 43,933 asymptomatic nondiabetic men with a mean age of 44 years, who were free of known CVD at baseline.[19] A total of 595 stroke events occurred during 702,928 person-years of follow-up. Age-adjusted fatal, nonfatal, and total stroke event rates per 10,000 person-years for normal FPG (80 to 109 mg/dL), impaired fasting glucose (110 to 125 mg/dL), and undiagnosed diabetes (≥126 mg/dL) are listed in **Table 28-3**. For FPG levels of 110 mg/dL or greater, each 10-unit increment of FPG was associated with a 6% higher risk of total stroke events ($P = .05$).

TABLE 28-3 Stroke Rates per 10,000 Patient-Years in Different Levels of Fasting Plasma Glucose (FPG)

	NORMAL FPG (80-109 g/dL)	IMPAIRED FPG (110-125 mg/dL)	UNDIAGNOSED DIABETES (≥126 mg/dL)	SIGNIFICANCE
Fatal strokes	2.1	3.4	4.0	$P < .002$
Nonfatal strokes	10.3	11.8	18.0	$P < .008$
Total strokes	8.2	9.6	12.4	$P < .008$

Data from Sui X, Lavie CJ, Hooker SP, et al: A prospective study of fasting plasma glucose and risk of stroke in asymptomatic men, *Mayo Clin Proc* 86:1042-1049, 2011.

In another study of 14,000 patients with CHD, a J-shaped association was found between fasting glucose and incident stroke.[20] Stroke events after adjustment were increased in patients with fasting glucose levels of 100 to 109 mg/dL (OR 1.3), 110 to 125 mg/dL (OR 1.6), when compared with levels of 90 to 99 mg/dL. However, patients with very low fasting glucose levels (<80 mg/dL) also exhibited a 1.5-fold increased risk of stroke. The mechanisms underlying this association remain unclear.

In 3127 patients with TIA or minor ischemic stroke in the Dutch TIA Trial,[21] a J-shaped relationship between baseline nonfasting glucose levels and stroke risk was also observed. In patients with impaired glucose tolerance (defined as glucose 7.8 to 11.0 mmol/L), risk of stroke was almost doubled compared with those with normal glucose levels (HR 1.8, 95% CI 1.1-3.0) and almost tripled in diabetic patients (glucose ≥11.1 mmol/L; HR 2.8, 95% CI 1.9-4.1). Patients with low glucose levels (<4.6 mmol/L) had a 50% increased stroke risk (HR 1.5, 95% CI 1.0-2.2) compared with those with normal glucose levels. There was no association between glucose levels and risk of MI or cardiac death. When impaired glucose tolerance was measured by oral glucose tolerance test (OGTT) as in the Japanese Hisayama study,[22] 2-hour values of the OGTT of 11.1 mmol/L were associated with a more-than-doubled risk for stroke (in men, HR 2.71; in women, HR 2.19).

Glycated hemoglobin concentrations are also associated with the risk of stroke even below diabetes thresholds. On analysis of nondiabetic adults participating in the community-based Atherosclerosis Risk in Communities (ARIC) study,[23] HbA1c concentrations—adjusted for potential confounders and for other vascular risk factors—of greater than 6% were associated with two to three times increased risk of stroke. The adjusted HRs for ischemic stroke according to baseline HbA1c are displayed in **Figure 28-2**.

A meta-analysis from 15 prospective cohort studies, which included 760,925 participants, tested the association of stroke risk with prediabetes defined in two ways. Among the eight studies that defined prediabetes as fasting glucose levels ranging from 100 to 125 mg/dL (5.6 to 6.9 mmol/L), which is the current American Diabetes Association (ADA) definition, there was no increase in the risk for stroke after adjustment for established cardiovascular risk factors (1.08; 95% CI 0.94-1.23). In contrast, among the five studies that used the ADA's more stringent 1997 definition of prediabetes (fasting glucose levels ranging from 110 to 125 mg/dL [6.1-6.9 mmol/L]), there was a 21% increased RR after adjustment for established cardiovascular risk factors (1.21; 95% CI 1.02-1.44; $P = .03$), indicating that the extent of the relationship between prediabetes and risk for stroke is a matter of definition of prediabetes.[24]

For those studies that included data on impaired glucose tolerance or combined impaired glucose tolerance and impaired fasting glucose, there was an increased risk for stroke after adjustment for established cardiovascular risk factors (1.26; 95% CI 1.10-1.43; $P < .001$).

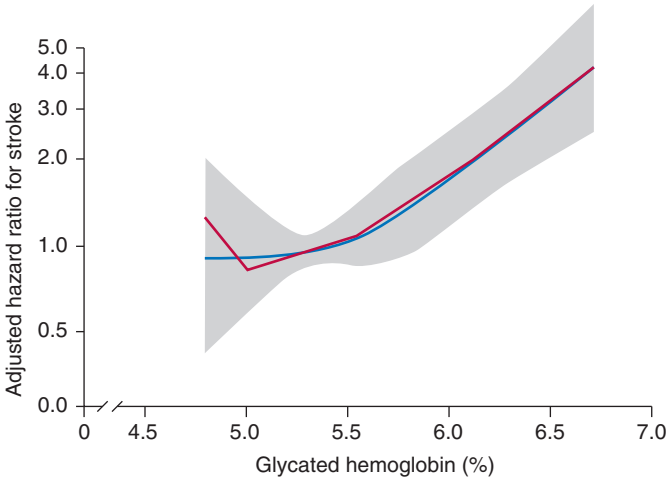


FIGURE 28-2 Adjusted hazard ratios for ischemic stroke according to baseline glycated hemoglobin. *(Modified with permission from Selvin E, Steffes MW, Zhu H, et al: Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults,* N Engl J Med *362:800-811, 2010.)*

Metabolic Risk Configurations (Insulin Resistance, Metabolic Syndrome, Adiposity)

Insulin resistance (IR), a state in which cells fail to respond to the normal actions of insulin, has also been found to be associated with an increased risk of stroke. In the Cardiovascular Health Study,[25] individuals without prevalent diabetes or stroke at baseline were followed for 17 years. Higher IR measured with the Gutt index[26] or 2-hour postload glucose levels was associated with a higher stroke incidence. For calculation of the Gutt index (insulin sensitivity index), plasma glucose and insulin concentrations from fasting (0-min) and 120-minute samples from the OGTT are used. The index is defined as follows:

$$\text{MCR}/\log \text{MSI}$$

The metabolic clearance rate (MCR) is obtained by $\text{MCR} = m/\text{MPG}$, where MPG is the mean of the 0- and 120-min glucose values from the OGTT. The mean serum insulin (MSI, mU/L) is the mean insulin concentration obtained from the 0- and 120-min samples of the OGTT.

The glucose uptake rate in peripheral tissues, m (mg/min), is obtained by the following formula:

$$m = [75{,}000\,\text{mg} + (\text{Glucose}_0 - \text{Glucose}_{120}) \times 0.19 \times \text{BW}]/120\,\text{min}$$

where the term (0.19 × BW) denotes glucose space, and BW is body weight (kg).

The RR for the lowest quartile versus the highest quartile of the Gutt index was 1.64 (95% CI 1.24-2.16), adjusted for demographics and prevalent cardiovascular and kidney



disease. Similarly, the adjusted risk ratio (RR) for the highest quartile versus the lowest quartile of 2-hour glucose was 1.84 (95% CI 1.39-2.42). In contrast, the adjusted RR for the highest quartile versus the lowest quartile of fasting insulin was not significant (1.10; 95% CI 0.84-1.46).

Higher levels of IR are associated with a 10% to 100% increased risk of stroke, depending on the degree of elevation and on the presence of other associated vascular risk factors. The U.S. National Health and Nutrition Examination Survey (NHANES) revealed the homeostatic model assessment of insulin resistance (HOMA-IR; equation: Fasting glucose [mmol/L] × Fasting insulin [mU/L]/22.5) as a measure for insulin resistance[27] to be independently and significantly associated with stroke risk with an OR of 1.06 (95% CI 1.01-1.12) for each HOMA-IR unit, after adjustment for age, history of MI, the presence of hypertension or claudication, activity level, and HbA1c.[28] It seems clear that IR is a risk factor for stroke, but it remains controversial whether insulin concentrations themselves or markers of glucose tolerance convey the highest risk.

The role, and impact of the metabolic syndrome (MetS), a clustering of disturbed glucose and insulin metabolism, obesity, and abdominal fat distribution, dyslipidemia, and hypertension remain controversial. A Finnish population-based cohort study on stroke risk[29] with an average follow-up of 14.3 years revealed for men a 2.41-fold (95% CI 1.12-5.32) increased risk for ischemic stroke associated with MetS, after adjustment for socioeconomic status, smoking, alcohol, and family history of CHD. After additional adjustments the results remained significant.

In the Northern Manhattan Study, 3298 stroke-free individuals were prospectively followed for 6.4 years with a 44% prevalence of MetS, which was associated with a 50% increase in stroke risk after adjustment for sociodemographic and risk factors.[30] The effect of MetS on stroke risk was greater in women (HR 2.0; 95% CI 1.3-3.1) than in men (HR 1.1; 95% CI 0.6-1.9) and among Hispanics (HR 2.0; 95% CI 1.2-3.4) compared with blacks (HR 1.3; 95% CI 0.7-2.3) and whites (HR 1.28; 95% CI 0.6-2.5).

A contrary result was found in a Greek study with a 10-year follow-up,[31] in which MetS per se at baseline or combinations of its components did not predict the development of ischemic stroke in patients with type 2 diabetes. After statistical calculations, only waist circumference (HR 1.006) and age (HR 1.061) were significant predictors for stroke risk. However, habits of food consumption and the influence of the Mediterranean diet in the Greek population were not considered.

Also, in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial,[15] which analyzed the effect of treatment with atorvastatin versus placebo in reducing stroke in patients with a recent stroke or TIA, patients with MetS were not at increased risk for stroke or major cardiovascular events, but more frequently had revascularization procedures (adjusted HR 1.78; 95% CI 1.26-2.5; $P = .001$).

The difference in the results of epidemiologic studies compared with an intervention study such as SPARCL might be a result of the effect of intensive risk factor management for patients enrolled in clinical drug trials. For example, during the SPARCL trial, blood pressure—as a component of MetS—and other risk factors were carefully controlled, and all persons received appropriate antithrombotic treatment, which is usually not reliably the case for those included in epidemiologic studies.

All together, the available data support the consideration of MetS as an independent risk factor for stroke, depending on the metabolic and vascular risk configuration of the affected person on the whole and depending on the definition of MetS. The fact that the incremental stroke risk associated with MetS appears greater than the sum of its components suggests potential biologic interaction among MetS components, generating a risk that is more than additive. According to the type of study and the definition of MetS, its relation to increased risk of stroke is most commonly statistically significant.

The methodologic problems of such association studies with MetS are also obvious, if one notes the variability of the proportion of patients with diabetes included, which ranged from 0% to 100%: the Northern Manhattan Study[30] had a proportion of 17% with diabetes; in the Finnish study[29] no patients with diabetes were included; and the Greek study[31] analyzed a group with 100% prevalence of diabetes. However, all studies similarly analyzed and reported the "independent" contribution of MetS to the risk of stroke.

Obesity in most studies is associated with an increased risk of stroke, whether measured by body mass index (BMI), waist-to-hip ratio, waist-to-height ratio, or waist circumference.[32] Persons with a BMI of 30 kg/m^2 or more have a twofold risk of stroke compared with individuals with a BMI of less than 23 kg/m^2.[33] According to the results of a collaborative analysis of 57 prospective studies with 900,000 individuals, each unit increase in BMI is associated with an increase in the adjusted risk of stroke by approximately 6%. Among adults who are overweight or obese (BMI 25 to 50 kg/m^2), each 5 kg/m^2 increase in BMI is associated with an approximately 40% higher mortality rate from stroke (HR 1.39; 95% CI 1.31-1.48).[34] In the INTERSTROKE study,[12] persons with a waist-to-hip ratio in the highest tertile had a 65% increased risk of stroke (OR 1.65, 99% CI 1.36-1.99) compared with those in the lowest tertile.

However, all measures of adiposity and obesity such as BMI, waist-to-hip ratio, and waist circumference do not consistently improve prediction of stroke risk when added to the most robustly associated stroke risk factors such as arterial hypertension and diabetes. Despite these often discordant observations, excess adiposity remains a major modifiable determinant of these causal risk factors for stroke.

PATHOPHYSIOLOGY AND SUBTYPES OF ISCHEMIC STROKE IN DIABETES

Stroke in diabetes is the clinical culmination of atherosclerotic changes in the extracranial and intracranial large and small arteries associated with hyperglycemia. The proatherogenic effects in diabetes on cerebral blood vessels are not different from effects on coronary arteries and encompass advanced glycation endproducts (AGEs), oxidative stress, endothelial dysfunction, inflammation, and hypercoagulability. In addition, the increased rate of CHD among patients with diabetes causes cardiomyopathy and AF, both of which predispose to cardioembolic stroke. AF is responsible for at least 20% to 30% of ischemic strokes.[35] Recent findings indicate that AF may be relatively common in diabetic patients, with the risk of AF increased by 30% to 40% in individuals with diabetes.[36] The severity of cardioembolic strokes and the resulting disability are greater than with noncardioembolic stroke, and hospital mortality is doubled.

A recent U.S. cohort study comparing 17,372 patients with diabetes with age- and gender-matched patients without

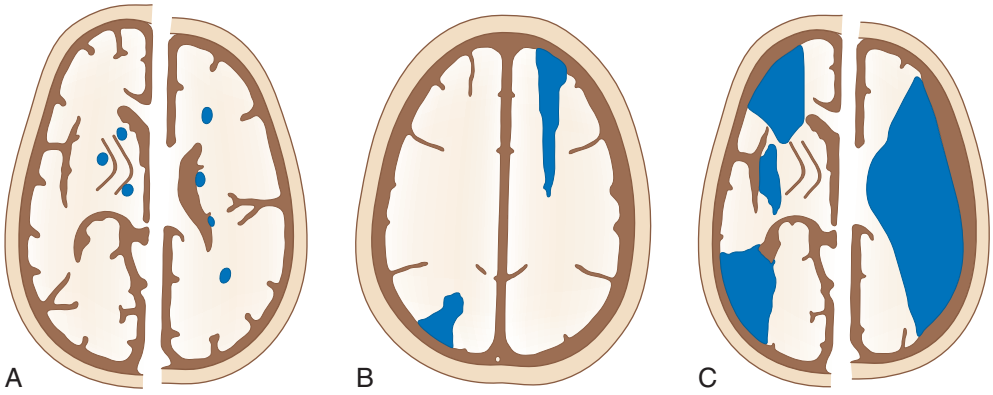


FIGURE 28-3 Diabetes increases the risk for all subtypes of ischemic stroke: **A,** lacunar; **B,** hemodynamic by large artery occlusion; and **C,** cardioembolic.

type 2 diabetes[37] found a significantly higher prevalence of AF among patients with versus without diabetes (3.6 versus 2.5%). Over a mean follow-up of 7.2 ± 2.8 years, diabetic patients without AF at baseline developed AF at an age- and gender-adjusted rate of 9.1 per 1000 person-years (95% CI 8.6-9.7) compared with a rate of 6.6 (95% CI 6.2-7.1) among nondiabetic patients. After full adjustment for other risk factors, diabetes was associated with a 26% increased risk of AF in women (HR 1.26; 95% CI 1.08-1.46), but diabetes was not a statistically significant factor in men (HR 1.09; 0.96-1.24). Diabetes not only is a risk factor for developing AF, but also increases the risk of its systemic and cerebral embolic complications. Depending on other accompanying risk factors, stroke rates in AF can reach almost 20% per year. Diabetes is one of the risk items counting as one point in the six-point $CHADS_2$ score and the nine-point CHA_2DS_2-VASc score, both of which are used to calculate an individual's stroke risk in AF and to inform clinical decision making with regard to antithrombotic therapies.

Because of its impact on cerebrovascular and cardiac systems, diabetes incrementally increases risk for all three subtypes of ischemic stroke: lacunar, large artery occlusive, and thromboembolic. The distribution of these stroke subtypes among patients with diabetes is similar to that in the general population; however, those with diabetes have a greater burden of small-vessel, or lacunar, infarcts, which sometimes are clinically silent.[38] In addition, the proportion of ischemic strokes with infratentorial localization is relatively increased in patients with diabetes (**Fig. 28-3**).

PRIMARY AND SECONDARY PREVENTION OF STROKE IN DIABETES

Glucose Control

In the 1441 patients with type 1 diabetes (aged 13 to 40 years) enrolled in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study,[39] intensive glucose management for 6.5 years reduced the risk of cardiovascular composite events (nonfatal MI, stroke, or cardiovascular deaths) significantly by 57% over a mean follow-up period of 17 years, compared with individuals under conventional treatment. However, the absolute numbers of stroke were low, with only one event in the intensive treatment group and five in the conventional treatment group. The target preprandial blood glucose in the intensively treated group was 70 to 120 mg/dL (<180 mg/dL postprandial); the mean HbA1c values were approximately 2% lower than in the conventional treatment group (7.4% versus 9.1%).

In patients with type 2 diabetes in the UKPDS study,[40] intensive treatment with sulfonylureas or insulin did not significantly reduce cardiovascular outcomes compared with conventional diet therapy. However, in the substudy within the UKPDS in which obese patients received metformin as a first-line treatment, the risk of stroke was reduced by 42% compared with the group receiving conventional treatment (3.3 versus 6.2 events per 1000 patient-years).[41]

Three more recent large long-term trials (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE]; Action to Control Cardiovascular Risk in Diabetes [ACCORD]; Veterans Affairs Diabetes Trial [VADT]) also compared the effects of intensive versus standard treatment in individuals with longstanding type 2 diabetes and a fairly high risk of cardiovascular and cerebrovascular events.[42–44] In the ADVANCE and the VADT studies, no difference in cardiovascular outcomes—including stroke—could be found between the two glucose-lowering strategies. In the ACCORD study the rates of nonfatal stroke were similar in the intervention and control groups.

No beneficial effects of tight glucose management over a mean period of 5 years could be found in a meta-analysis of 34,533 patients with type 2 diabetes (HR 0.96; 95% CI 0.83-1.1).[45] A similar result was communicated in a Cochrane review summarizing the findings from 29,986 patients with type 2 diabetes from 20 randomized trials.[46] The duration of intervention varied from 3 days to 12.5 years. Targeting intensive glycemic control did not reduce the RR of nonfatal stroke (risk ratio 0.96; 95% CI 0.8-1.2).

Taken together, to date, insufficient data are available to prove that intensive and tight glycemic control per se improves occurrence of stroke—in particular in type 2 diabetes. Treatment of patients with a high risk of stroke must balance the risk of recurrent hypoglycemia against the potential advantages of lower targets of HbA1c.

Management of Diabetes Associated Vascular Risk Factors

In the UKPDS, the variables that predicted the 188 incident strokes in DM included duration of diabetes, age, gender, smoking, systolic blood pressure (SBP), dyslipoproteinemia, and the presence of AF. Modifiable risk factors for stroke accompanying diabetes have been targeted for stroke prevention in several randomized controlled trials.

Hypertension

Hypertension has long been recognized as the major modifiable risk factor for stroke. Lowering of blood pressure has a large effect on the risk of stroke. In the UKPDS, better blood pressure control among patients with type 2 diabetes was associated with a 44% reduction in stroke incidence for each 10–mm Hg reduction in mean SBP.[47] In a meta-analysis of 13 trials with 37,736 patients with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance, more intensive blood pressure control in comparison with standard treatment was associated with a 10% relative reduction in all-cause mortality and a 17% reduction in stroke (OR 0.83; 95% CI 0.73-0.95).[48] The stroke-preventing effect of blood pressure lowering was mainly detected in those trials, in which the target of SBP was 130 to 135 mm Hg. Tighter blood pressure control below the threshold of 130 mm Hg was associated with a significant reduction in stroke, but a 40% increase in serious adverse events, with no benefit for cardiac, renal, and retinal complications.

In the ACCORD trial, a total of 4733 participants with type 2 diabetes were randomly assigned to intensive blood pressure treatment targeting a systolic pressure of less than 120 mm Hg, or standard therapy targeting a systolic pressure of less than 140 mm Hg.[49] After 1 year, a mean SBP of 119.3 mm Hg was achieved in the intensive therapy group and 133.5 mm Hg in the standard therapy group. The annual risk rates of stroke after a mean follow-up of 4.7 years were 0.32% and 0.53% in the two groups, respectively (HR 0.59; 95% CI 0.39-0.89). However, the intensive blood pressure management did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events and led to an increase in adverse events such as syncope and hyperkalemia.

A recent meta-analysis of 11 studies with 42,572 participants compared the effects of tight SBP control (target SBP <130 mm Hg) versus usual SBP control (SBP 130 to 139 mm Hg) on stroke prevention in general[50] and in subgroups. Achieving a tight SBP level was associated with a significant 20% lower stroke risk (RR 0.80; 95% CI 0.70-0.92). The subgroup of patients with cardiovascular risk factors but without established CVD showed substantial reduction of future stroke risk with tight control (RR 0.49; 95% CI 0.34-0.69), but those with established CVD at entry did not experience stroke risk reduction with tight control (RR 0.92; 95% CI 0.83-1.03). Patients with DM at entry showed reduction of future stroke risk with tight control, but those without DM at entry only experienced marginal stroke risk reduction with tight control (RR 0.65, 95% CI 0.48-0.87; versus RR 0.85, 95% CI 0.73-1.00).

Most guidelines for stroke prevention recommend a blood pressure less than 130/80 mm Hg. Reaching these target levels is probably more important than the choice of antihypertensive drug. However, for stroke prevention, beta blockers seem to be inferior to other antihypertensives and, in contrast, calcium channel blockers have been shown to be superior. As a potential explanation for such observed differences in efficacy in stroke prevention by drug classes, different effects on within-individual blood pressure variability across the classes have been proposed, which seems to be an independent risk predictor for stroke (**Fig. 28-4**).[51]

Lipids

In a subgroup of 6000 patients of the Heart Protection Study with diabetes, simvastatin at a daily dose of 40 mg versus placebo was associated with a 28% (95% CI 8-44) reduction in ischemic stroke, independent of baseline lipid levels.[52] The Collaborative Atorvastatin Diabetes Study (CARDS) found a 48% (95% CI 17-52) reduction in all types of stroke in patients with type 2 diabetes without manifest CVD in the intervention group with 10 mg atorvastatin daily compared with placebo.[53] The Cholesterol Treatment Trialists' Collaboration meta-analysis of 18,686 people with diabetes included 14 placebo-controlled randomized trials of statins.[54] There was a significant 21% (95% CI 7-33) reduction of first stroke, which was similar to the effect observed in the 71,370 patients without diabetes.

For secondary stroke prevention, fewer data are available. The SPARCL trial found that atorvastatin 80 mg daily versus placebo reduced stroke risk in patients with recent stroke or TIA and no known CHD by 16% with a 5-year absolute reduction in stroke risk of 2.2%[55] In the secondary analysis of the SPARCL trial for the subgroup of individuals with type 2 diabetes and MetS, no treatment-by-subgroup interactions were found, indicating a similar stroke preventive effect for the subgroup of patients with diabetes.[55]

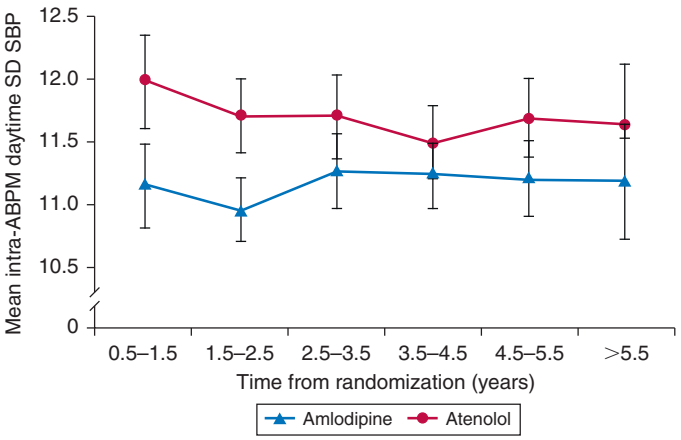


FIGURE 28-4 Lower variability in daytime systolic blood pressure (standard deviation [SD]) of the calcium-channel blocker amlodipine compared with the beta blocker atenolol. A higher blood pressure variability was an independent risk factor for stroke. *(Modified from Rothwell PM, Howard SC, Dolan E, et al: Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke,* Lancet Neurol *9:469-480, 2010.)*

Platelet Inhibition

In a meta-analysis on the use of aspirin for primary prevention in persons with diabetes, no significant benefits could be recorded with respect to reduction of serious vascular events, including stroke (RR for stroke 0.83, 95% CI 0.60-1.14).[56] For secondary prevention of stroke, no major studies specifically for individuals with diabetes have been performed. Although a subgroup analysis of the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial suggested a slightly greater benefit of clopidogrel versus aspirin for patients with diabetes,[57] the meta-analysis of the Antithrombotic Trialists' Collaboration[58] found a similar stroke reduction for both cardiovascular events and ischemic stroke.

Although there is no clear proof for a substantial effect of platelet inhibition on the risk of stroke in primary prevention, antiplatelet agents—mostly aspirin—should be considered for every patient with diabetes identified to be at increased risk of future cerebrovascular complications.

Multifactor Risk Factor Management

The efficacy of multifactorial preventive measures on the risk of stroke in individuals with type 2 diabetes was assessed in three trials.[59–61] No clear benefits specifically for stroke prevention were found in the Euro Heart Survey on Diabetes and the Heart, apart from a general 40% risk reduction in cardiovascular events.[59] Cerebrovascular revascularization procedures, however, were reduced by half. The ADDITION-Europe trial, which focused on early multifactorial treatment after diagnosis of diabetes versus usual care, did not find a different stroke rate between the groups during a mean follow-up of 5.3 years, but the stroke rate was low in both groups with only 1.3% and 1.4%, respectively.[61] A small 17% nonsignificant reduction in the incidence of cardiovascular events and death was observed.

In contrast, a substantial benefit of multifactorial management was found in the Steno-2 trial,[60] in which the 7.8-year multifactorial approach encompassed the use of statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, platelet inhibition, glucose control, and lifestyle modification. At the end of the 13.3 years of follow-up, among 160 high-risk individuals with longstanding type 2 diabetes and microalbuminuria who participated in the study, a reduction in cardiovascular events by 59% (HR 0.41; 95% CI 0.25-0.67] was found. The number of all types of stroke was reduced by 80% (6 versus 30 events) (**Table 28-4**). These findings underscore that multifactorial risk factor management may be the key for a substantial reduction of stroke in diabetes.

Oral Anticoagulation in Atrial Fibrillation in Patients with Diabetes

Twenty percent to 30% of ischemic strokes are caused by cardiac embolism, most commonly from the left atrium and its appendage in nonvalvular AF. Diabetes, together with previous stroke, hypertension, advancing age, congestive heart failure, female gender, and atherosclerosis, is one of the major risk factors for stroke in individuals with AF (see the discussion of pathophysiology and subtypes of ischemic stroke in diabetes) and counts for 1 point in the six-point $CHADS_2$ score and the nine-point CHA_2DS_2-VASc score, both of which are used for the calculation of an individual´s stroke risk in AF (**Tables 28-5** and **28-6**).

Primary stroke prevention with adjusted-dose warfarin, a vitamin K antagonist (VKA), with a target international normalized ratio (INR) of 2.0 to 3.0, reduces the RR of first-ever stroke in individuals with AF with a moderate vascular risk profile by approximately two thirds compared with placebo (annual stroke risk 1.8% versus 4.6%), without a statistically significant increase in the annual rates of intracranial hemorrhage (0.4% versus 0.2%) or major extracranial bleeding (approximately 2% versus 1%). For secondary stroke prevention, warfarin with a target INR of 2.0 to 3.0 also reduces the risk of recurrent stroke significantly by approximately two thirds compared with placebo (annual stroke risk 3.9% versus 12.3%; HR 0.34, 95% CI 0.20-0.57) and is associated with an annual nonsignificant increase in major bleeding (2.8% versus 0.7%; HR 3.20, 95% CI 0.91-11.3).[62]

Aspirin is not an adequate strategy to replace warfarin and is associated with a nonsignificant reduction in the RR of stroke by approximately 20% compared with placebo (5.2% per year with aspirin versus 6.3% with placebo; RR 0.81, 95% CI 0.65-1.01).[63] For patients with AF and previous ischemic stroke or TIA, aspirin did not show a significant reduction in risk of recurrent stroke compared with placebo (10% per year with aspirin versus 12% with placebo; HR 0.86, 95% CI 0.64-1.15).[64]

Particularly in older patients, aspirin is often prescribed with the assumption that it will cause fewer bleeding complications than warfarin. However, not only is aspirin not efficacious in stroke prevention in AF, but it also causes a similar rate of intracranial bleeding compared with warfarin. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial compared warfarin and aspirin in patients aged 75 years or older with a 14% prevalence of diabetes, and demonstrated a twofold increased stroke rate with aspirin versus warfarin without a significant difference in major intracranial or extracranial hemorrhage (1.9% versus 2.0%).[65]

TABLE 28-4 Numbers of Events after 13.3 Years with Intensive Versus Conventional Multifactorial Cardiovascular Risk-Modifying Therapy among 160 High-Risk Patients with Diabetes

	INTENSIVE THERAPY (NUMBER OF EVENTS)	CONVENTIONAL THERAPY (NUMBER OF EVENTS)
Death from any cause	24	40
Myocardial infarction	9	35
Stroke	6	30
All cardiovascular events	51	158

TABLE 28-5 Conditions and Points for Calculation of the CHA_2DS_2-VASc Score (Maximum 9 Points)

C	Congestive heart failure (or left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mm Hg (or treated hypertension on medication)	1
A_2	Age 75 years or older	2
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischemic attack or thromboembolism	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65 to 74 years	1
Sc	Sex category is female	1

TABLE 28-6 Annual Stroke Risk According to CHA_2DS_2-VASc score

CHA_2DS_2-VASC SCORE	STROKE RISK %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Data from Lip GY, Frison L, Halperin JL, et al: Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort, *Stroke* 41:2731-2738, 2010.



Despite its great efficacy in stroke prevention, oral anticoagulation with VKAs such as warfarin is sometimes poorly managed; register data show that only approximately 50% to 70% of suitable patients receive adequate anticoagulant treatment. And even when treatment is administered, the achieved "time in therapeutic range"—which ensures sufficient stroke protection and a low number of serious bleeding events—is generally poor and does not exceed a proportion of 50% to 60%.[64]

Three newer direct oral anticoagulants (DOACs) have been proven to be successful competitors with warfarin. The direct thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors rivaroxaban and apixaban were shown in large prospective trials to be at least as efficacious and safe as warfarin. The corresponding trials were the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, in which 23% of the patients had diabetes[66]; the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), in which 40% had diabetes[67]; and the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial, in which 20% had diabetes,[68] respectively. These three DOACs so far tested in clinical trials have all shown noninferiority in stroke prevention compared with VKAs, with better safety, consistently limiting the number of intracranial hemorrhages. In the subgroups of patients with diabetes or who otherwise are at high risk for stroke in the three studies, similar results with respect to efficacy and serious bleeding side effects were found, compared with the entire study populations. Rivaroxaban is taken once daily, whereas dabigatran and apixaban have twice-daily dosage regimens. Some drug interactions are evident with the DOACs; patients with severe renal impairment were excluded from the trials, and, in particular, dabigatran has a high renal clearance.

A recent meta-analysis of the mentioned studies analyzing the subgroup of patients with previous stroke or TIA showed that in 14,527 patients, DOACs were associated with a significant reduction of annual stroke or systemic embolism (OR 0.85, 95% CI 0.74-0.99; RR reduction 14%; absolute risk reduction, 0.7%; number needed to treat (NNT) = 134 over 1.8 to 2.0 years) compared with warfarin. DOACs were also associated with a significant reduction in major bleeding compared with warfarin (OR 0.86; 95% CI 0.75-0.99; RR reduction, 13%; absolute risk reduction, 0.8%; NNT = 125), mainly driven by the significant reduction of hemorrhagic stroke (OR 0.44; 95% CI 0.32-0.62; RR reduction 57.9%; absolute risk reduction 0.7% per year; NNT = 139).[69]

The advantages of the DOACs are predictable anticoagulant effects without the need for monitoring coagulation, low propensity for drug interactions, and lower rates of intracranial hemorrhage than with warfarin. Disadvantages might be the short half-life, which in noncompliant patients causes regression to normal coagulation, and until now the absence of specific antidotes. There is a need for standardized tests that accurately measure plasma concentrations and anticoagulant effects. Other disadvantages are possibly higher rates of gastrointestinal hemorrhage and greater expense than with warfarin. With DOACs it is possible that an increasing number of patients with AF who are at risk of stroke—including individuals with diabetes—will be optimally anticoagulated, and consequently the burden of AF-related stroke can be reduced. The guidelines of the European Society of Cardiology of 2012 recommend the DOACs as being broadly preferable to VKA in the vast majority of patients with nonvalvular AF,[70] and a similar recommendation has been provided by the American Heart Association and American Stroke Association.[71]

Carotid Artery Interventions in Diabetes: Carotid Endarterectomy and Carotid Artery Stenting

Carotid artery stenosis is one of the macrovascular complications of diabetes. The presence of an atherosclerotic stenotic lesion in the extracranial internal carotid artery or carotid bulb has been associated with an increased risk of stroke. Randomized trials have shown that carotid endarterectomy (CEA) in appropriately selected patients with carotid stenosis modestly reduces stroke risk compared with patients treated by medical management alone.

However, the risk of stroke in patients undergoing intensive contemporary medical treatment has fallen significantly since the mid-1980s. Recent estimates suggest that the stroke risk in patients undergoing contemporary best medical treatment is overlapping that of patients who have undergone surgery in historical randomized trials, such that the advantages of CEA demonstrated in older trials in such patients are the subject of present controversy.[72,73] According to the guidelines of the American Stroke Association, patients with asymptomatic carotid artery stenosis should receive lifestyle interventions and treatment of all vascular risk factors. Prophylactic CEA performed with less than 3% morbidity and mortality is regarded as useful in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound).

The usefulness of carotid artery stenting (CAS) as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is uncertain.

For secondary stroke prevention in patients with high-grade internal carotid artery stenosis, CEA has proved its effectiveness, but it has not exclusively been investigated in patients with diabetes. In CEA, both periprocedural and long-term risks are higher in patients with diabetes than without; for example, pooled data[74] from the European Carotid Surgery Trial (ECST)[75] and North American Symptomatic Carotid Endarterectomy Trial (NASCET)[76] found a significant 1.45 periprocedural risk of complications for patients with versus without diabetes (9.7% versus 7.0%; RR 1.45; 95% CI 1.05-2.02).

However, the advantages of the surgical intervention have also been shown in subgroups of patients with diabetes. Three major prospective randomized trials (ECST, NASCET, Veterans Affairs Cooperative Study [VACS])[77] have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with an atherosclerotic carotid stenosis greater than 70% (on angiography). The absolute risk reduction with CEA for the subgroup of patients with diabetes was 16% (95% CI 6.0-27.4), higher than for the overall study cohort with absolute reduction of 13.5% (95% CI 9.1-17.9).

Pooled analysis of these trials, including more than 3000 symptomatic patients, found a combined 30-day stroke and death rate of 7.1% in surgically treated patients. There is a controversy for patients with symptomatic stenosis of 50% to 69%. In the NASCET trial of symptomatic patients with a stenosis of 50% to 69%, the 5-year rate of any ipsilateral stroke was 15.7% in patients treated surgically compared

with 22.2% in those treated medically. Thus, to prevent one ipsilateral stroke during the 5-year follow-up, 15 patients would have to undergo CEA. The conclusions justify use of CEA only with appropriate case selection when the risk-benefit ratio is favorable for the patient. Patients with a moderate (50% to 69%) stenosis who are at reasonable surgical and anesthetic risk may benefit from an intervention performed by a surgeon with excellent operative skills and a perioperative morbidity and mortality rate of less than 6%.

CAS has emerged as a therapeutic alternative to CEA for treatment of symptomatic extracranial carotid artery occlusive disease; it seems to be advantageous because of its less invasive nature, decreased patient discomfort, and a shorter recuperation period.

However, two randomized trials, the French EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis)[78] and European SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy)[79] trials, had to be stopped prematurely for reasons of safety and futility because of a higher 30-day stroke and death rate in the CAS group. In the EVA-3S trial, for example, the 30-day combined stroke and death rate for CAS was 9.6% compared with 3.9% for CEA, with an RR of 2.5 for any stroke or death for CAS compared with CEA. Both trials have been criticized for possible inadequate and nonuniform operator experience, which may have had a negative impact on CAS performance and associated clinical outcomes.

The most recent Carotid Revascularization Endarterectomy Versus Stent Trial[80] (CREST), in which 30% of patients had diabetes, found no significant difference in the composite primary outcome (30-day rate of stroke, death, MI, and 4-year ipsilateral stroke) in patients treated with CAS compared with CEA (7.2% with CAS versus 6.8% with CEA; HR with stenting, 1.11; 95% CI 0.81-1.51). In symptomatic patients, the 4-year rate of stroke or death was nonsignificantly different—8% with CAS compared with 6.4% with CEA. In symptomatic patients, the rate of any periprocedural stroke or postprocedural ipsilateral stroke was significantly higher in the CAS group than in the CEA group (5.5% versus 3.2%). However, in symptomatic patients the rate of MI was significantly higher in the CEA group (2.3% versus 1.0%). For the entire study population, a significant qualitative interaction between age and treatment efficacy was found: for patients older than 70 years, CAS showed greater efficacy, whereas for patients younger than 70 years, CEA results were superior (**Table 28-7**).

In the long-term observation of the CREST study, rates of restenosis or occlusion after CAS or CEA at 2 years showed no significant difference, with 6.0% of patients who had undergone CAS versus 6.3% of those who had undergone CEA developing restenosis or occlusion (HR 0.90, 95% CI 0.63-1.29). Diabetes was the strongest independent predictor of restenosis or occlusion after both procedures, with a 2.31-fold (95% CI 1.61-3.31) increased risk.

Based on these data, the guidelines of the American Stroke Association[81] recommend CEA for patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, if the perioperative morbidity and mortality risk is estimated to be below 6%. For a lower degree of stenosis (50% to 69%), CEA is recommended depending on patient-specific factors, such as age, gender, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be below 6%. In patients with stenosis with a degree greater than 50%, no indication for carotid revascularization exists. If surgical revascularization is performed, it should be within 2 weeks after the stroke or TIA. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% on noninvasive imaging or by more than 50% on catheter angiography. In patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, when medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered. CAS in the these settings is held to be reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%.

Mechanical Revascularization of Severe Intracranial Arterial Stenosis

Patients with a recent cerebrovascular event and severe stenosis (70% to 99%) of major intracranial arteries are at high annual risk of approximately 23% for recurrent stroke in the territory of the stenotic artery, despite treatment with aspirin and standard management of vascular risk factors. As a promising prevention strategy, percutaneous transluminal angioplasty and stenting (PTAS) was suggested. The self-expanding Wingspan stent was approved by the Food and Drug Administration (FDA) for use in patients with atherosclerotic intracranial arterial stenosis. Despite the mechanically attractive and therefore feasible way of revascularization, PTAS was not proved to be useful when compared with aggressive medical management of such intracranial stenosis. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial[82] tried to overcome this uncertainty, but the enrollment was halted after 451 randomized patients because of the high risk of stroke or death within 30 days of enrollment in the PTAS arm relative to the medical arm. Of the participants, 46% had type 2 diabetes. The 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) almost threefold higher than in the medically managed group with 5.8% (nonfatal stroke, 5.3%; non–stroke-related death, 0.4%). Beyond 30 days, stroke in the same brain territory occurred in 13 patients in each group. An analysis of

TABLE 28-7 Endpoint Events According to Treatment Group in the CREST Trial

	PERIPROCEDURAL PERIOD			FOUR-YEAR STUDY PERIOD (INCLUDING PERIPROCEDURAL PERIOD)		
	CAS	CEA	HR for CAS versus CEA (95% CI)	CAS	CEA	HR for CAS versus CEA (95% CI)
Death	0.7%	0.3%	2.25 (0.69-7.30)	11.3	12.6	1.12 (0.83-1.51)
Any Stroke	4.1%	2.3%	1.79 (1.14-2.82)	10.2	7.9	1.40 (1.04-1.89)

patient and procedural factors that may have been associated with periprocedural cerebrovascular events in the trial found that diabetes was one of the major factors that were significantly associated with ischemic events, with an OR of 4.5 (95% CI 1.3-16.1) associated with diabetes. Based on this study, in severe intracranial stenosis, the following composition of aggressive medical management is recommended: aspirin at a dose of 325 mg/day; clopidogrel at a dose of 75 mg/day for the first 90 days after the incident event; management of the primary risk factors such as elevated SBP and elevated low-density lipoprotein (LDL) cholesterol levels; and management of secondary risk factors (diabetes, elevated non–high-density lipoprotein (non-HDL) cholesterol levels, smoking, excess weight, and insufficient exercise) with the help of a lifestyle modification program. The corresponding targets of intervention were SBP of less than 140 mm Hg (<130 mm Hg in patients with diabetes), and an LDL cholesterol level of less than 70 mg/dl. Thus, stenting in intracranial stenosis cannot be recommended at this time.

HYPOGLYCEMIA AND STROKE

The brain is directly and rapidly affected by a critical decrease in blood glucose because its metabolism relies exclusively on glucose supply. In this context, repeated episodes of severe hypoglycemia are thought to contribute to the development of cognitive decline and dementia, because of their cumulative neurotoxic effect (see the later discussion of diabetes as a vascular risk factor for cognitive impairment and dementia).

However, hypoglycemia may also cause adverse cerebrovascular events. Acute hypoglycemia provokes profound physiologic changes affecting the cardiovascular system and several hematologic parameters, as a consequence of sympathoadrenal activation and counter-regulatory hormonal secretion. Many of these responses have an important role in protecting the brain from neuroglycopenia, through altering regional blood flow and promoting metabolic changes that will restore blood glucose to normal. Some of these effects are potentially pathophysiologic, and in people with diabetes who have not yet developed endothelial dysfunction, they may have an adverse impact on a vasculature that is already damaged. The acute hemodynamic and hematologic changes may increase the risk of localized tissue ischemia, and major vascular events can certainly be precipitated by acute hypoglycemia. These include myocardial and cerebral ischemia, and occasionally infarction. The possible mechanisms underlying these hypoglycemia-induced cerebrovascular effects include hemorrheologic changes, white cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines. Therefore it is suggested that acute and repeated hypoglycemia could aggravate cerebrovascular complications associated with diabetes by enhancing atherosclerotic vascular and proembolic changes.[83]

DIABETES AND ACUTE STROKE—POSTSTROKE HYPERGLYCEMIA

Epidemiology and Definition of Poststroke Hyperglycemia

If one analyzes the patient characteristics in acute stroke studies, approximately one fifth of patients have diabetes. The prevalence of DM ranges from 10.6% (MAST-E study) to 24.4% (SAINT-II study,; CLASS] study). In the large study of systemic thrombolysis in acute ischemic stroke, ECASS-3), the prevalence of diabetes was 15.7%.[84] Other epidemiologic data suggest the prevalence of diabetes to be 10% to 20% among patient populations with acute stroke, not accounting for a number of undiagnosed cases of diabetes that also must be assumed.

Poststroke hyperglycemia occurs not only in the acute stroke phase in patients with preexisting DM, but also in patients without a prior diagnosis of diabetes. PSH can occur in all subtypes of strokes. The frequency found in various studies depends on the following:

1 The definition of the threshold of hyperglycemia (fasting glucose from 6.0 mmol/L to 7.8 mmol/L)

2 The definition of the duration of the acute poststroke period (12 to 96 hours)

3 The frequency of blood glucose testing (single test on admission versus repeated single tests versus continuous glucose monitoring)

4 The nutritional status of patients (no nutrition versus parenteral nutrition versus intravenous nutrition)

With a glucose limit value of 7.0 mmol/L, the frequency of PSH is approximately 40% to 50%,[85,86] at least twice as high as the diabetes prevalence in stroke patients. In a study with continuous glucose monitoring, Allport and colleagues were able to demonstrate that PSH can have a dynamic progression. After an initial peak, blood glucose levels were lower approximately 14 to 16 hours later; this was followed by a second hyperglycemic peak 48 to 69 hours later.[85] More recent studies,[87,88] however, could not show this "two-peak" dynamic. Various patterns were shown with respect to latency and duration of PSH, namely "initial" or "delayed" PSH peaks as well as permanent hyperglycemia. The PSH pattern distribution varied significantly between patients with and without diabetes; whereas patients with diabetes more frequently had permanent hyperglycemia, patients without diabetes more frequently had initial PSH peaks (**Table 28-8**).[88] Only 15% of patients with diabetes but 70% of those without diabetes showed a permanent normoglycemic state within 24 hours poststroke.

This possible variability of PSH over time explains that frequencies and patterns of PSH in various studies depend on the respective times of glucose measures. This makes it difficult to interpret and compare different studies.

Causes of Poststroke Hyperglycemia

If one takes the previously described prevalence rates, half of PSH patients have a preexisting disturbance of glucose

TABLE 28-8 Distribution of Patients With and Without Diabetes in the Four Progression Patterns of Poststroke Hyperglycemia

	DIABETES (n=161) N (%)	NO DIABETES (n=587) N (%)
Initial hyperglycemia	21 (13%)	79 (13%)
Hyperglycemia after 24 hours	16 (10%)	54 (9%)
Persistent hyperglycemia	100 (62%)	46 (8%)
Persistent normoglycemia	24 (15%)	408 (70%)

Data from Yong M, Kaste M: Dynamic of hyperglycemia as a predictor of stroke outcome in the ECASS-II trial, *Stroke* 39:2749-2755, 2008.

metabolism such as diabetes or prediabetes. In nonpreexisting diabetes, a postulated cause of PSH is a neurometabolic "stress hyperglycemia" with the activation of the hypothalamus-pituitary-adrenal (HPA) axis with the release of cortisol and adrenaline and subsequent glycolysis and gluconeogenesis.[89] However, this theory may be too global and simplified. There are contradictory endocrinologic findings in reference to the "stress postulates" because some studies could not prove the claimed stress metabolism.[90]

Neurotoxicity in Poststroke Hyperglycemia

The findings with regard to neuronal damage mechanisms of PSH are mainly the result of experimental studies performed on animals and a few patient examinations with functional cerebral imaging. These have shown that there is not one singular damage mechanism, but rather there are a coaction and an interaction of various "neurotoxic" effects. **Table 28-9** summarizes the potential direct and indirect mechanisms of neuronal damage by hyperglycemia during the acute phase of ischemic stroke.[91–93]

Poststroke Hyperglycemia as a Global Negative Outcome Predictor

In animal models, the extent of hyperglycemia in acute cerebral ischemia determined the size of cerebral lesions and mortality. In patient studies, the negative prognostic impact of hyperglycemia was identified after adjustment for other variables such as age, severity, and extent of the stroke.[94] A meta-analysis based on 32 clinical trials[95] found a relative 93% increase for the in-hospital or 30-day mortality rates in patients with PSH on admission (unadjusted OR 1.93; 95% CI 1.15-3.24). It is interesting to note that the negative effect of PSH in clinical studies was lower in patients with diabetes, with a nonsignificant unadjusted OR for in-hospital or 30-day mortality of 1.3 (95% CI 0.49-3.43), compared with those without diabetes, with an OR of 3.07 (95% CI 2.5-3.79). Despite the large heterogeneity of the studies that were part of this meta-analysis, even after subgroup analyses the negative predictive value of PSH in patients without prevalent diabetes remained stable with an increased risk of 41% for an unfavorable clinical outcome in a relatively homogeneous group of patients with cerebral ischemia (OR 1.41; CI 1.16-1.73). Even more recent studies, such as one conducted at the Mayo Clinic,[96] found that glucose levels of more than 7.2 mmol/L led to a significantly more severe clinical progression of the stroke and was associated with a risk of mortality that was 2.3 times higher. Even in this study, the PSH in patients without diabetes had a significantly greater negative effect than in those with diabetes; the increase in mortality associated with PSH was 3.4-fold in nondiabetic patients, compared with 1.6-fold in patients with diabetes. The data from the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA) register for strokes allowed extraction of PSH as a significant negative predictor for hospital mortality, with a significant OR of 1.066 (95% CI 1.028-1.104). With regard to the cognitive prognosis, PSH proved to be nonnegative predictive, which was confirmed by another study that dealt exclusively with this question; however, the case number of 113 is low.[97]

In general, the negative implications of PSH have not been studied specifically with regard to the various types of strokes. However, there are indications that PSH does not necessarily have an unfavorable effect in small lacunar infarctions or even could be favorable in terms of prognosis. The analysis of the patient population participating in the studies with the neuroprotectant lubeluzole (LUB-INT-9 and LUB-INT-5])[98] showed that glucose levels in excess of 8 mmol/L within 6 hours after the stroke event coincided with larger infarctions with an expected lower functional outcome (OR 0.60; 95% CI 0.41-0.88), whereas in lacunar ischemia the chance for a good functional outcome was almost three times better (OR 2.70; 95% CI 1.01-7.13). However, this positive correlation turned negative with higher glucose levels (>12 mmol/L) (**Fig. 28-5**).

The prospective Spanish multicenter observational study Glycaemia in Acute Stroke (GLIAS)[99] examined the question concerning a critical predictive threshold value of PSH in 476 acute stroke patients with mean glucose levels of 7.6 ± 3.2 mmol/L and demonstrated a statistically calculated predictive cut-off value of 8.6 mmol/L, both initially as well as within the first 48 hours, which differentially predicted between a good and a bad outcome after 3 months. After multivariable statistical adjustment, any hyperglycemia above this limit value was associated with a risk of unfavorable progression that was 2.7 times higher (95% CI 1.42-5.24) and a mortality risk that was 3.8 times higher (95% CI 1.79-8.10). There were no differences between those with and without prevalent diabetes. This correlation could be demonstrated not only in larger but also in smaller infarctions. Finally, the presently available evidence is contradictory in terms of the significance of isolated increased glucose levels compared with continuous increases.

TABLE 28-9 Hyperglycemic Damage Mechanisms in Acute Ischemic Stroke

Parenchyma toxicity (anaerobic/glucose metabolism)	Acidosis Lactate accumulation Increase of the NMDA receptor–dependent cellular calcium flux Inflammation Increased formation of free radicals Increased expression of matrix metalloproteinase 9 (MMP-9)
Vascular damage and perfusion defect	Endothelial dysfunction Reduced vessel reactivity Inflammation Prothrombotic state—for example, activation of plasminogen activator inhibitor 1 (PAI-1) Reduced NO production
Impairment of the blood-brain barrier	Edema formation Increased rate of hemorrhage
Noncerebral effects	Immune system Shift in fluid balance Disruption in peripheral perfusion
Consequences of the insulin deficit	Increased formation of free fatty acids with prothrombotic effect and reduction in vessel reactivity

MMP-9 = Matrix metalloproteinase 9; NMDA = *N*-methyl-D-aspartate; PAI-1 = plasminogen activator inhibitor 1.

Influence of Diabetes on Acute Stroke Treatments

Diabetes and PSH have been linked to a lower efficacy of intravenous thrombolysis with alteplase in ischemic stroke

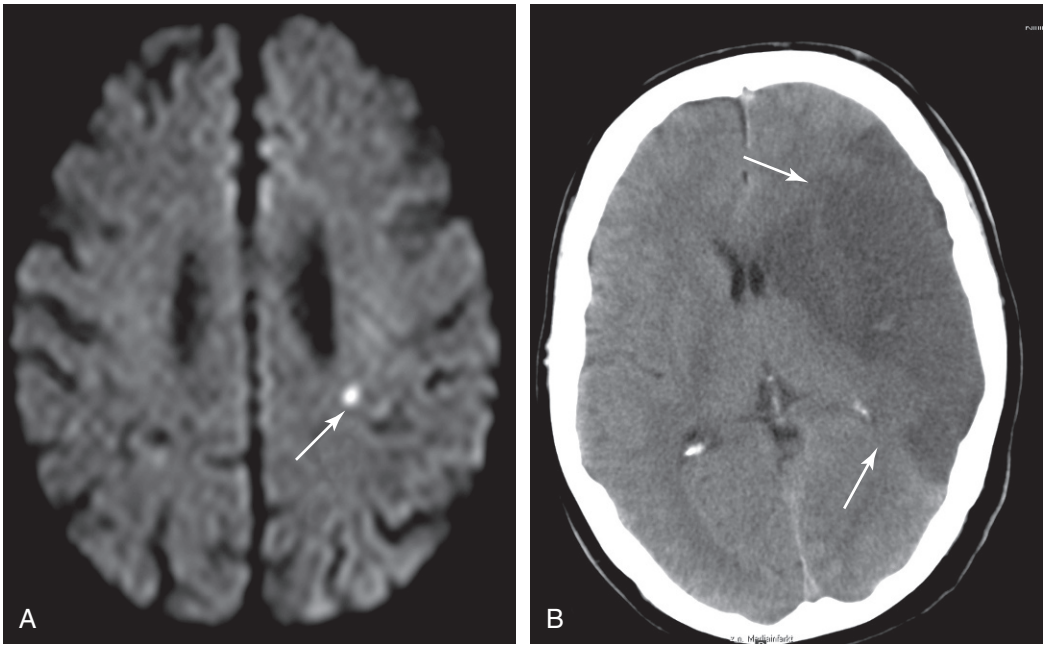


FIGURE 28-5 In small lacunar infarctions (**A,** white dot in the diffusion-weighted magnetic resonance imaging scan; white arrow), poststroke hyperglycemia has a less negative effect on functional outcome than in large territorial infarctions (**B,** large, dark gray infarction demarcation between the two white arrows in the computed tomography scan).

patients, resulting from both lower rates of recanalization and increased rates of complicating symptomatic intracerebral hemorrhage (SICH).[100,101]

In a multivariable analysis of 16,049 patients from the SITS-ISTR (Stroke Registry) of thrombolysis patients,[102] increasing blood glucose levels were independently, linearly, and significantly associated with a higher mortality and disability, and an increased risk of SICH. In particular, blood glucose from 181 to 200 mg/dL were associated with a threefold increased risk levels of SICH compared with the reference level of normoglycemia. The trends of associations between blood glucose and outcomes were similar in patients with diabetes (17% of the cohort) or without such history, except for mortality and SICH, in which the association was not statistically significant in patients with diabetes (mortality $P = .23$; SICH $P = .06$).

In Europe, patients with PS and concomitant DM were excluded from treatment with the approval of systemic intravenous thrombolysis with alteplase. Because of the uncertainty of its benefit-risk ratio in patients with diabetes, thrombolysis is often withheld in many such patients. An analysis of 29,500 patients from SITS-ISTR[103] compared with nonthrombolysed controls from the Virtual International Stroke Trials Archive (VISTA) registry, including 18.5% with diabetes, found a significant 45% better functional outcome (measured by the change in distribution of the modified Rankin Scale score 0 to 6) in the thrombolysed patients compared with controls among the subset of patients with diabetes (adjusted OR for a better outcome = 1.45 [95% CI 1.30-1.62]). This degree of benefit is comparable to the outcome relationship between thrombolysis and control groups among patients without diabetes (OR for a better outcome with thrombolysis = 1.53; 95% CI 1.42-1.63). Hence, outcomes with thrombolysis are better than controls among patients with diabetes, indicating no statistical justification for the exclusion of patients with diabetes who are otherwise eligible from receiving thrombolytic therapy in acute ischemic stroke.

Glucose-Lowering Treatment of Poststroke Hyperglycemia

Feasibility of Glycemic Control in Poststroke Hyperglycemia

There is no consensus regarding the best type of glycemic control, the best method for achieving it, and the necessary monitoring in the setting of acute stroke. The mentioned fluctuating course of PSH includes the risk of induced hypoglycemia when strict control is attempted. The type of insulin delivery has differed in reported studies; for example, whereas intravenous glucose-insulin-potassium (GIK) infusions were administered in the intervention study Glucose Insulin in Stroke Trial (GIST-UK),[104] other studies used staggered perfusion rates of insulin in NaCl 0.9% strictly applied according to the measured glucose levels, or they used 5% glucose or insulin in individual intravenous bolus dosages. One study from Glasgow involving 13 patients[105] showed the basic feasibility of a strict decrease in increased values by approximately 1 to 2 mmol/L with only one observed hypoglycemic event. There was no correlation between the better control of glycemia and any clinical success; however, the number of patients was clearly too low to address such a question. In the THIS) study,[95] which compared 46 diabetic patients with a glucose level of more than 8.3 mmol/L treated for 72 hours with an aggressive intravenous insulin infusion (N = 31; glucose target value <7.2 mmol/L) with conventional glycemia control with use of subcutaneous insulin (N = 15; glucose target value <11.1 mmol/L), the achieved mean glucose levels were significantly lower in the group undergoing targeting of strict control (7.4 mmol/L) than in the group treated subcutaneously (10.5 mmol/L). However, 11 patients (35%) became hypoglycemic in the aggressively treated group, and four of them (13%) were symptomatic; no hypoglycemia occurred in the group of patients undergoing conventional glycemia control (N = 15). In addition, the number of patients did not allow evaluation of any clinical low effects on the prognosis in this group, as well. A more recent

study[106] concluded that the control of glycemia with various regimens was difficult to achieve, particularly postprandial regimens because of discontinuous nutrition. This demonstrated that it is basically possible to lower the blood glucose levels to a normal range with aggressive intravenous insulin therapy during the first 24 to 72 hours after an ischemic infarction; however, the consequence is a not-insignificant number of hypoglycemia events. Although no lasting negative clinical consequences of hypoglycemia were evident, it seems imperative to monitor glucose levels closely.

Does Tight Glycemic Control Improve Outcome in Poststroke Hyperglycemia?

The previous recommendations to lower increased glucose levels during the acute phase of a stroke follow the plausible speculation that control of a clearly negative predictive risk factor should lead to an improvement in the clinical prognosis. However, until 2007 there were insufficient data from large prospective randomized studies with clinical endpoints to confirm this assumption. This gap was at least in part closed by the GIST-UK study,[104] which could not prove a positive endpoint effect of a target value–oriented glycemic control strategy and the results of which lead to large controversies regarding the practical consequences concluded from the data. In the active treatment group (GIK infusion) a mean blood glucose of 0.57 mmol/L was achieved, compared with patients treated with only physiologic saline solution; however, there were no differences between the groups in the primary or secondary endpoints. It is interesting that even in the NaCl infusion group, the blood glucose levels decreased significantly, which may correspond to the spontaneous progression of PSH (**Fig. 28-6**). In addition, the intervention arm showed significantly lower SBP values—on average 9 mm Hg lower.

First responses to the study questioned the efficacy of global control of glycemia. However, a number of limitations and methodologic problems of the GIST-UK trial warrant consideration. In 2005, it was discontinued after 7 years of recruitment after only 933 patients were included instead of the planned 2355 patients, which undermined the statistical power of the trial. In addition, the intervention was relatively delayed in its initiation and the glucose control achieved was not very pronounced—only 0.57 mmol/L lower in a population with initially moderate PSH. In addition, the unintended lowering of the blood pressure in the active treatment arm could have a negative effect on the endpoints. Therefore the results are unable to contradict the general target of an ambitious glycemic control including the avoidance of hypoglycemia.

The controversies of glycemic control in acute stroke are similar to those ongoing in the context of management of surgical and medical intensive care patients. If the clear results of a 34% reduction in mortality by tight glycemic control in the single-center study from University of Leuven[107] initially led to propagation of the use of such intensive glucose management, then newer results, in which the tight glycemic control with an achieved target value of 4.5 to 6.0 mmol/L[108] proved disadvantageous, have cast doubt on the value of tight glycemic control. However, for the treatment of acute strokes, the results of the GIST study cannot mean that lowering the glucose level in a patient who has sustained an acute stroke is discredited globally as superfluous. In connection with this, a trend toward such laissez-faire behavior can already be observed. The GLIAS results[99] allow speculation that there is a U-shaped curve of correlation between the prognosis and the blood glucose level. Accordingly both hypoglycemic and near-hypoglycemic values would be just as negatively predictive as significantly hyperglycemic values, and the best prognosis would be within the moderately hyperglycemic and normoglycemic ranges. If the hypothesis for such a correlation were to be tested prospectively, it remains plausible that lowering glucose levels from the moderately hyperglycemic to the hypoglycemic range would have a negative effect, whereas interventions to lower hyperglycemia to less-severe hyperglycemia or to normoglycemia could have a favorable effect on clinical outcomes. It is probable that the effectiveness of glycemic control is decisively dependent on the quality of glucose monitoring and the avoidance of hypoglycemia.

The guideline recommendations in Europe versus the United States differ in details, however, they both agree in a defensive manner to such a plausible assumption. The European Stroke Organisation (ESO) recommends lowering the glucose level with insulin if the values exceed 10 mmol/L (180 mg/dL), whereas the American Stroke Association prefers an intervention if the values exceed 140 mg/dL (approximately 7.8 mmol/L). The problem with these recommendations is that although they suggest an

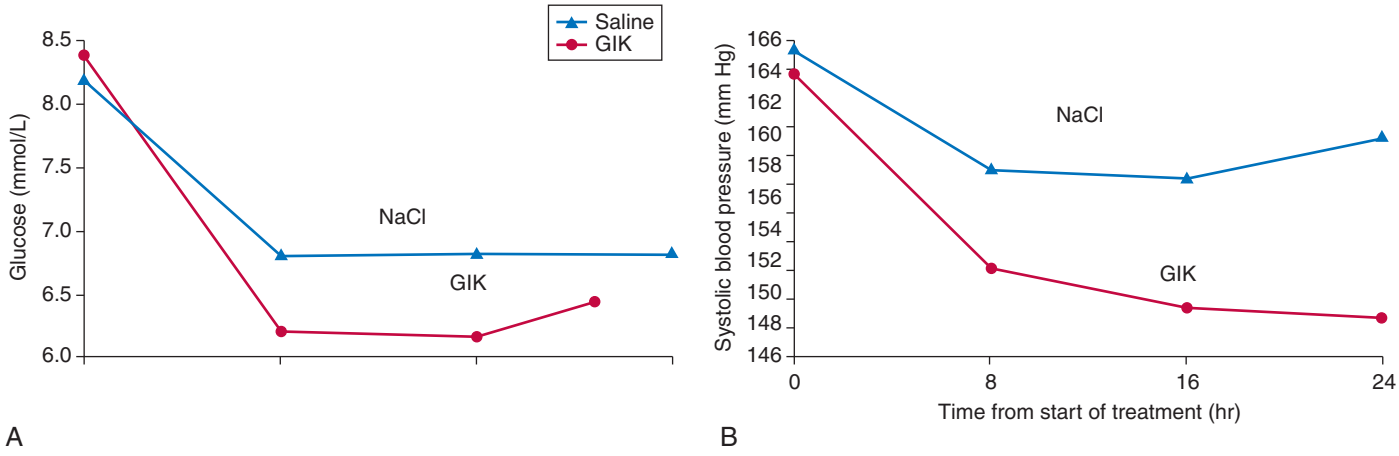


FIGURE 28-6 Mean glucose levels **(A)** and systolic blood pressure values **(B)** initially and 8, 16, and 24 hours later in both study arms of the GIST-UK study. GIK = Glucose-potassium-insulin infusion. *(Modified from Gray CS, Hildreth AJ, Sandercock PA, et al: Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Modified from* Lancet Neurol *6:397-406, 2007.)*

upper intervention limit for initiation of the intervention and advocate avoidance of hypoglycemia, neither guideline suggests a target glucose range. Now, it could be assumed that the recommended intervention thresholds are too high and the success of the intervention depends decisively on the avoidance of hypoglycemia; however, the data from clinical studies is insufficient to affirm such an approach.

DIABETES AS A VASCULAR RISK FACTOR FOR COGNITIVE IMPAIRMENT AND DEMENTIA

Because type 2 diabetes doubles the risk of stroke, and stroke alone causes cognitive impairment by strategic cognition-relevant brain lesions in approximately 20% of patients, a statistical and clinical association between diabetes and cognitive impairment is expected. However, brains of patients with diabetes, in addition to having the obvious cerebrovascular pathology, may also be affected by neurodegenerative cerebral pathology, leading to dementia. Although the influence of diabetes on cognitive function has been suggested since the 1930s and a large number of studies have been done in this area since then, no consensus has emerged regarding the role of diabetes in the development of dementia or whether optimal blood glucose control yields a protective effect. In general, the association between type 2 diabetes and dementia seems to be stronger for VD than for AD, but these observations are inconsistent.

Definition and Epidemiology

Type 2 diabetes disproportionally affects older adults in whom dementia is also a common condition. Large population-based studies examining people at an older age (>70 years) demonstrate that patients with type 2 diabetes are overrepresented among individuals with dementia. Dementia is one of the most devastating diseases of late life; approximately 4.6 million new cases of dementia are estimated to occur worldwide every year, and the prevalence of dementia is expected to quadruple by the year 2050 in the United States.

AD is the most common form of dementia, accounting for approximately 80% of all cases, followed by VD. So-called "mixed dementia" describes a combination of clinical and radiologic features of AD and VD. The proportion of these major types of dementia depends on criteria used for the differentiation, which vary widely. Diabetes has been linked not only to the full picture of dementia, but also to more subtle forms of cognitive impairment below the threshold of dementia, defined by neuropsychological testing. People with mild cognitive impairment are at increased risk of developing dementia, although the conversion rates reported range from 1% to 25% or more per year.[109] The determination of cognitive deficits and the diagnosis of the type of dementia are also not always easy. Thus the boundaries among cognitive deficit, early dementia, and more severe stages of dementia are sometimes difficult to discern.

DM is associated with cognitive dysfunction and has been related to accelerated cognitive decline in older adults, development of mild cognitive impairment, and increased risk of dementia, including both AD and VD (**Fig. 28-7**).

The association between DM and risk of mild cognitive impairment and dementia is robust, and diabetes also seems to increase the risk of progression from such impairment to dementia.

Clinical Studies

Cognitive decline in nondemented patients with diabetes has been studied in several cross-sectional case-control studies. Most of them show worse cognitive performance in patients across age groups between 50 and 80 years with type 2 diabetes compared with age-, gender-, and education-matched controls with regard to different cognitive features such as verbal memory, information processing speed, perception, visuoconstruction, language attention, and executive functioning.[110] Cross-sectional population-based

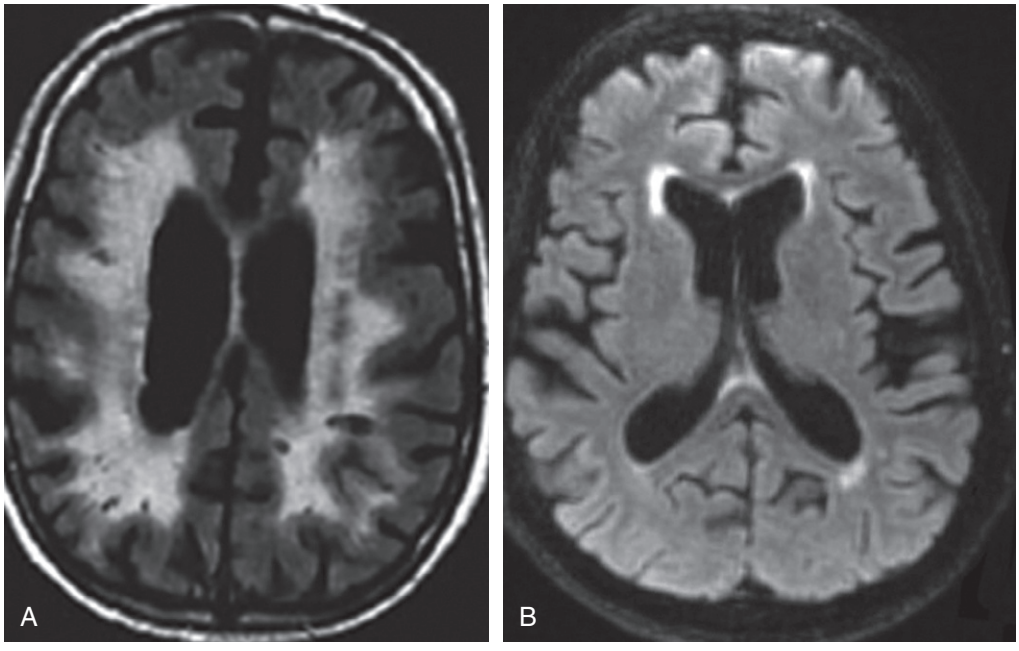


FIGURE 28-7 Magnetic resonance imaging scans of patients with diabetes-related types of dementia. **A,** A patient with vascular dementia with extensive white matter lesion and lacunar infarctions *(black holes).* **B,** A patient with only small white matter lesions but pronounced brain atrophy.

cohort studies such as ARIC[111] and the Framingham study[112] reported findings similar to those of most of the case-control studies. There seems to be a 1.5-fold increased risk for patients with type 2 diabetes for development of mild cognitive impairment.[113] Not all studies, however, observed significant differences in cognitive performance between patients with diabetes and controls despite elaborate cognitive testing and relatively large sample sizes.[114]

Some large longitudinal studies that examined the impact of diabetes on cognitive function reported cognitive decline over an average period of 5 years that exceeded the effects of normal aging by a factor of 1.5 to 2.17.[115] However, in most studies only a limited number of cognitive test results were affected and the absolute magnitudes of the observed differences were small and clearly distinct from the rate of decline that is typical for pathologic conditions such as AD. Other studies did not observe accelerated cognitive decline in patients with type 2 diabetes.[115] Taken together, the findings of these studies show relatively subtle decrements in cognitive functioning, which slowly progress over time.

However, according to the results of a systematic review of a large number of studies, type 2 diabetes is a risk factor for cognitive impairment crossing the threshold to dementia.[116,117] Type 2 diabetes is associated with a twofold to fourfold increased risk of VD and a 1.5- to 2-fold increased risk of AD. However, in studies, differentiation between the dementia subtypes of VD and AD is difficult, especially when it is based only on a clinical diagnosis. Moreover, many patients may be affected by both vascular and neurodegenerative pathology.[118] On the basis of these numbers, 6% to 8% of all cases of late-life dementia would be attributable to type 2 diabetes. Patients with type 2 diabetes were overrepresented by a factor 1.5 to 2 in subgroups of older individuals (age 65 years and older) with severe cognitive deficits.[113]

In some longitudinal studies, a longer diabetes duration and higher HbA1c levels were predictors for a faster development of cognitive decline.[113,116]

As with the relationship between prediabetic metabolic abnormalities and stroke, cognitive decrements have also been found in prediabetic stages and its vascular risk escorts such as hyperinsulinemia, impaired glucose tolerance, and MetS. They are all associated with an approximately 1.5- to 2-fold increased risk of development of cognitive impairment or dementia.[113,117,119]

Similarly, as with the relationship between diabetes and stroke, additional vascular risk factors and predispositions that are associated with type 2 diabetes (e.g., hypertension, dyslipoproteinemia, depression, stroke, genetics, demographic and lifestyle characteristics) may modulate or mediate cognitive functioning. One longitudinal study, for example, found that cognitive functioning in patients with type 2 diabetes was related to long-term exposure to hypertension, even in prediabetic stages.[120] In a group of middle-aged patients with diabetes, dyslipidemia was associated with worse declarative memory performance.[121] Many of these diabetes-associated risk factors are interrelated, and it therefore remains difficult to assess the exclusive impact of diabetes differentiated from the other risk factors on cognition.

Genetic predisposition might contribute to the association among type 2 diabetes, cognitive decrements, and dementia. The most widely examined risk factor is the apolipoprotein E (apo E) ε4 allele, an important risk factor for CVD and late-onset AD in the general population. Some studies have shown interaction effects between type 2 diabetes and the apo E ε4 allele, further aggravating the diabetes-associated risk of cognitive decline and dementia,[113] whereas others could not confirm such an interaction.[122] Another genetic relationship between type 2 diabetes and AD may be mediated by the insulin-degrading enzyme, which degrades both insulin and amyloid beta, the main component of amyloid plaques and pathologic hallmark of AD. Variations in the insulin-degrading enzyme gene were associated with an increased risk of type 2 diabetes and AD.[123] It is interesting to note that these associations were only observed in individuals who do not carry the apo E ε4 allele.

Brain Imaging Studies

Brain imaging studies have been used to analyze vascular lesions including infarcts, white matter hyperintensities (WMHs) and microbleeds, and cerebral atrophy as possible structural correlates of impaired cognition in type 2 diabetes. According to the increased risk of stroke in diabetes, it is not surprising that population-based studies found a 1.5- to 2-fold higher prevalence and incidence of lacunar infarcts associated with diabetes.[124] The relationship between type 2 diabetes and WMHs is less clear. Several large population-based studies did not observe a significant association between diabetes and WMHs,[125] whereas others observed a modest increase in WMH severity and accelerated WMH progression in patients with type 2 diabetes through use of elaborate WMH scaling and volumetry.[113,116] Some studies identified microbleeds on T2-weighted magnetic resonance imaging (MRI) scans, a marker of cerebrovascular disease, to be more prevalent in patients with type 2 diabetes.[126]

Modest degrees of global and focal cerebral atrophy in patients with diabetes have been reported from cross-sectional studies. Findings of atrophy in specific brain regions such as the frontal or medial temporal lobe, including the hippocampus and amygdala—a typical pattern in AD—suggest a possible association between type 2 diabetes and neurodegenerative brain changes and dementia.[124]

Autopsy Studies

In line with the findings from imaging studies, autopsy studies in patients with diabetes have revealed an approximately 2.5-fold increased risk for cortical and subcortical cerebral infarctions and Alzheimer pathology.[116] Diabetes was also associated with changes in the cerebral microvasculature, including amyloid angiopathy and capillary basement thickening. In contrast, no link has been demonstrated between type 2 diabetes and the severity of Alzheimer-typical amyloid plaques and neurofibrillary tangles.[127,128] Some studies have even reported a reverse association, with a decreased amount of Alzheimer pathology in patients with diabetes.[129] In the Honolulu-Asia Aging Study, no relationship between type 2 diabetes per se and the amount of plaques and tangles was observed; however, there was an interaction between type 2 diabetes and the presence of the apo E ε4 allele, showing that patients with type 2 diabetes who carried the apo E ε4 allele had a higher number of plaques and tangles than nondiabetic apo E ε4 carriers.[130] Thus, the current evidence from autopsy studies does not confirm a direct link between diabetes and Alzheimer pathology, but several

possible interactions. Just as much, it is possible that diabetes-associated vascular pathology may lower the threshold at which Alzheimer-type pathology becomes clinically manifest.

Prevention and Treatment of Diabetes-Related Dementia

There is no evidence that approved medical treatments used in the treatment of AD such as cholinesterase inhibitors or *N*-methyl-D-aspartate (NMDA) receptor antagonists have a deviant effect on patients with versus without diabetes. However, the beneficial effects of antidementive medications are limited.

As yet, there is also no evidence-based disease-modifying treatment for diabetes-related cognitive decrements. However, there are some hints that modest cognitive decrements in patients with type 2 diabetes are partially reversible with improvement of glycemic control,[131] although some studies found no such effect.[132]

The recently published ACCORD-MIND study, a nested substudy of the ACCORD trial comprising 2977 trial participants, followed various outcome parameters of brain function and structure. The Digit Symbol Substitution Test (DSST) score was used as a neuropsychological measure at baseline and at 20 and 40 months, and total brain volume (TBV) was assessed as a brain structure outcome measure with MRI at baseline and 40 months in a subset of participants.[133] The investigators found no significant treatment difference after 40 months in the mean DSST score between the groups randomized to more intensive versus standard glucose control. The intensive treatment group, however, had a significantly greater mean TBV than the standard treatment group (4.62 cm^3, 95% CI 2.0-7.3). The authors concluded that, in conjunction with the nonsignificant effects of more intensive glycemic control on other ACCORD outcomes and with the increased mortality in participants in the intensive treatment group, the findings of the study do not support the use of intensive therapy to reduce the adverse effects of diabetes on the brain in patients with similar characteristics to those of the study participants.

A current analysis sought to determine whether poor glucose control was related to worse cognitive performance in 3069 elderly individuals aged 70 to 79 years within a follow-up period of 10 years. There was a link between cognition and HbA1c levels, and the authors concluded that poor glucose control among those with diabetes is associated with worse cognitive function and greater decline, although the study was not a prospective interventional study.[83]

Multifactorial vascular risk factor intervention (hypertension, dyslipidemia, hyperglycemia, tobacco smoking) was found to slow cognitive decline in patients with preexisting AD in an observational study.[134]

Insulin therapy in patients with diabetes may also be effective in slowing cognitive decline in patients with preexisting AD. The investigators[135] compared oral glucose-lowering drugs alone versus a combination of oral drugs with insulin in 104 patients with mild-to-moderate AD and type 2 diabetes for a follow-up period of 12 months. Cognitive function, assessed by the Mini Mental State Examination (MMSE) worsened significantly from baseline by 56.5% in the oral therapy alone group compared with 23.2% in patients in the oral plus insulin group. Also, measurements with the scored Clinical Global Impression (CGI) survey instrument showed a significant worsening for all domains after 12 months in the oral medication group but not in the oral-insulin group. The two groups were matched for body mass index, serum lipids, triglycerides, apo E ε4 allele, and smoking status. After adjustment for imbalance in ischemic heart disease and hypertension, each with higher baseline prevalence in the oral-insulin group, the results remained significant.

A possible relationship between glucose-lowering drug treatment and dementia was detected with metformin treatment. One study in cellular models showed that metformin increases the production of amyloid beta through upregulation of beta-secretase,[136] and the authors raised the concern that metformin could increase the risk of AD. However, the findings of this study require replication, and the relevance of its findings to humans has not been demonstrated. Of note, clinical data published to date have been discordant, with some studies suggesting increased dementia among metformin users[137] and others finding the opposite.[138] The effect of metformin on cognition will be assessed in the ongoing phase II trial (NCT00620191) testing whether metformin can decrease cognitive decline and dementia in overweight persons aged 55 to 90 years with mild cognitive impairment.

One example of other approaches that have been examined with regard to impact on dementia is physical activity, which in observational studies assessing associations with light and moderate exercise was associated with better cognitive function in patients with type 2 diabetes.[139]

A surprising result was found in a French study of patients with AD with a mean age of 77 years, of whom those with type 2 diabetes showed a significantly lower rate of cognitive decline than did individuals without diabetes.[131] Causes for this paradox may include confounding factors such as a survival bias related to diabetes, but also different nutrition habits of cognitively impaired patients.

The Role of Hypoglycemia on Cognitive Impairment and Dementia

Assessing the role of hypoglycemia on cognitive disorders in patients with diabetes is complex, because the influence of hyperglycemia in the course of the diabetic metabolic disorder itself, its duration, and its vascular and degenerative complications interact to a great extent.

In type 1 diabetes, a meta-analysis[140] and results from DCCT and EDIC[141,142] did not provide evidence for an association between the occurrence of more hypoglycemic episodes in the intensive treatment group (**Table 28-10**) and impaired cognition in young adult patients.

In type 2 diabetes, two longitudinal studies examined the relationship between severe hypoglycemic events and cognitive decline. Data from the large diabetes registry of the Kaiser-Permanente Northern California Diabetes Registry showed a dose-response relationship between the number of severe hypoglycemic episodes and the risk of development of dementia up to 17 years after the events.[143]

In contrast, the Fremantle diabetes study[144] found no evidence that severe hypoglycemia contributes to cognitive decline in older patients with type 2 diabetes, but suggested a reverse direction of causality: People with dementia were at increased risk of further severe hypoglycemic episodes over the subsequent 5 years of follow-up. Thus, a bidirectional relationship between diabetes-associated hypoglycemia episodes and cognitive disturbances may be considered. Differential

TABLE 28-10 Number of Hypoglycemic Episodes During the Three Periods of the DCCT/EDIC Study

EPISODES	DCCT (6.5 YEARS)		EDIC FOLLOW-UP (12 YEARS)		18 YEARS FOLLOW-UP	
	Intensive treatment (N=588)	Conventional treatment (N=556)	Intensive treatment (N=588)	Conventional treatment (N=556)	Intensive treatment (N=588)	Conventional treatment (N=556)
0	364	445	465	424	326	365
1-5	190	104	119	127	212	175
>5	34	7	4	4	50	16

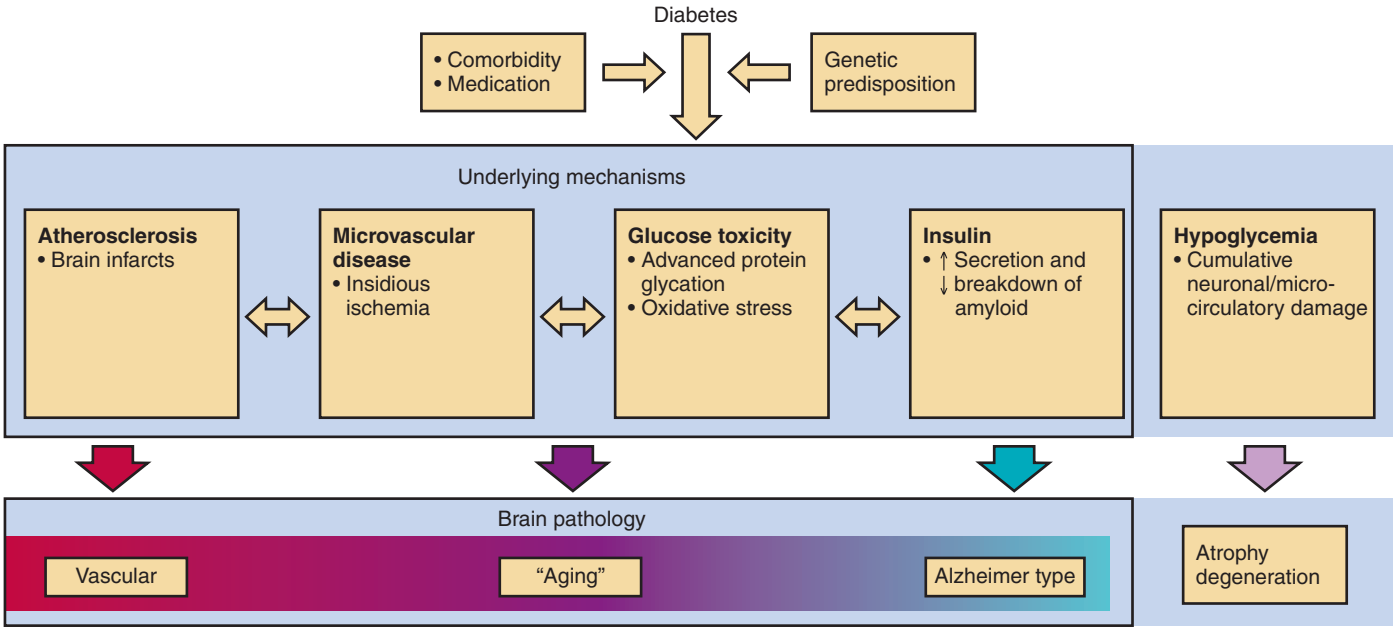


FIGURE 28-8 Proposed pathophysiologic interaction between diabetes and advanced brain aging or dementia including vascular mechanisms, glucose-mediated neuronal toxicity, interference with Alzheimer-typical cerebral amyloid deposition, and cerebral damage by episodes of hypoglycemia. *(Modified from Biessels GJ, Staekenborg S, Brunner E, et al: Risk of dementia in diabetes mellitus: a systematic review,* Lancet Neurol *5:64-74, 2006.)*

vulnerability of the brain to hypoglycemia in young and older patient populations may be another reason for the observed discrepancy in between type 1 and type 2 diabetes.[114,116]

Vascular and Degenerative Mechanisms in Diabetes-Related Dementia

Mechanisms through which type 2 diabetes may adversely affect cognitive function include vascular disturbances, glucose toxicity, hypoglycemic episodes, and disturbances of cerebral insulin signaling.[116] Diabetes could interact with the dementia process by accelerating the pathologic processes underlying AD, for example, through disturbances of amyloid metabolism or through vascular (co)morbidity.[145] An alternative explanation is that diabetes affects the reserve capacity of the brain, possibly through the same mechanisms that cause the subtle cognitive decrements, and thereby reduces the threshold for the neurodegenerative dementia process to become clinically manifest. As one potential non-cerebrovascular mechanism in the relationship between diabetes and dementia, peripheral hyperinsulinemia with impaired cerebral insulin signaling leading to a type of "cerebral IR" affecting amyloid-beta clearance in the brain has been suggested.[146] Another potential noncerebrovascular mechanism is elevation of AGEs in patients with type 2 diabetes, resulting in upregulation of the AGE receptor (RAGE), which may interfere with AD-related lipid metabolism in the brain.[113] Based on the proposed relationship between impaired insulin signaling in the brain and dementia, intranasal administration of insulin has been studied as a potential treatment for AD, with promising initial results.[147]

A summary of the discussed relationships between diabetes and dementia is shown in **Figure 28-8**.

SUMMARY

Patients with diabetes have a twofold to fourfold risk of ischemic stroke compared with patients without diabetes. This increased risk encompasses all four subtypes: ischemic, lacunar, large artery occlusive, and thromboembolic strokes. Comorbid vascular risk factors in patients with diabetes not only add to the stroke risk from diabetes, but multiplicatively affect this risk. The risk for cerebrovascular disease is already increased in prediabetic states

Interventional studies that focused exclusively on glucose control in patients with diabetes could not demonstrate a reduction in stroke rates. However, approaches using multifactorial risk factor management—including intensive glucose control—have shown a significant reduction in stroke rates. These findings underscore that multifactorial risk factor management may be the key for a substantial reduction of stroke incidence in patients with diabetes.

Acute stroke can generate acute disturbances of glucose metabolism with PSH, which is associated with an approximately twofold risk of an unfavorable outcome. Tight hyperglycemia management in acute stroke has not yet proven to

be beneficial, because in prospective studies its potential beneficial effect has been negatively compensated by high rates of hypoglycemic episodes.

In addition to increasing the risk of stroke, diabetes similarly leads to chronic and insidious damage of the brain, resulting in cognitive decline and dementia. Dementia in patients with diabetes results not only from cerebrovascular-mediated neuronal damage, but also from neurodegenerative processes manifesting as AD.

There are hints regarding a bidirectional relationship between diabetes and dementia. On the one hand, people with diabetes have double the risk of developing dementia; on the other hand, cognitive and behavioral manifestations of dementia lead to disturbances in glucose metabolism.

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29 Cardiovascular Autonomic Neuropathy

Paul Valensi

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Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes. CAN is usually detected at a subclinical stage by means of several cardiovascular autonomic reflex tests and may affect patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM). Poor glycemic control is a major determinant of this complication. CAN predicts a higher mortality and may induce significant cardiovascular changes in diabetic patients.

PATHOPHYSIOLOGY OF VAGOSYMPATHETIC IMBALANCE

The relationships between cardiac autonomic dysfunction and insulin resistance are complex. Each of them may aggravate the other (**Fig. 29-1**). Moreover, vagosympathetic imbalance may induce hemodynamic changes.

Role of Vagosympathetic Impairment in Insulin Resistance

Obesity is a major determinant of CAN in T2DM patients. Data suggest that cardiac autonomic dysfunction may occur in obese individuals before diabetes. In obese patients, cardiac vagal tests more often show impairment in those with the metabolic syndrome, and the impairment is more commensurate with the severity of perturbations of the components of the syndrome. In individuals with the metabolic syndrome, increased activity of the sympathetic nervous system was found to be associated with several of the components of the metabolic syndrome, including elevated blood pressure (BP).[1] However, whether this disorder contributes to the development of the metabolic syndrome or is a consequence of it remains still a matter of debate. Because cardiac autonomic dysfunction may occur in individuals with only one or two metabolic abnormalities without insulin resistance, cardiac autonomic dysfunction is suggested to precede insulin resistance in the metabolic syndrome.[2] This hypothesis is strongly supported by a recent demonstration that the progression to T2DM is associated with increased central sympathetic drive, blunted sympathetic responsiveness, and altered norepinephrine disposition.[3] Indeed, vagal depression and sympathetic predominance might contribute to insulin resistance and depression of insulin secretion. Several findings support this hypothesis. In obese normotensive patients, central fat distribution is associated with higher sympathetic activity.[4] Glucose usage has been found to correlate negatively with the low frequency–to–high frequency ratio (LF/HF) on spectral analysis of heart rate (HR) variations, which means that glucose usage was reduced when sympathetic activity was relatively higher.[5] We reported that in obese patients with vagal cardiac impairment, insulin levels correlated negatively with glucose oxidation rate (indirect calorimetry), suggesting a more severe insulin resistance that may again result from sympathetic overactivity.[6]

Effects of Insulin and Glucagon-like Peptide 1 on Autonomic Activity

Hyperinsulinemia subsequent to insulin resistance may also modulate autonomic activity and induce changes in hemodynamic parameters.[7] Insulin may increase HR slightly, as shown during hyperinsulinemic euglycemic clamps in healthy individuals.[8,9] HR elevation results from both vagal depression[8,9] and cardiac sympathetic activation as indicated by increased muscle sympathetic nerve activity (MSNA),[9,10] plasma catecholamines,[11] and in some studies[8] LF/HF ratio (an index for relative sympathetic predominance). Sympathoexcitatory effects of insulin result from a central nervous action and possibly from baroreflex activation secondary to insulin-induced peripheral vasodilation. However, during insulin clamp the shift in the cardiac

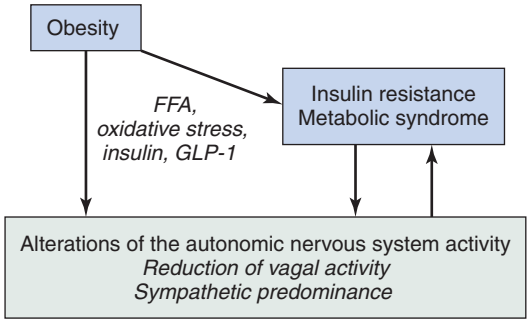


FIGURE 29-1 Relationships between cardiac autonomic dysfunction and obesity and insulin resistance. FFA = Free fatty acids; GLP-1 = glucagon-like peptide 1.

autonomic activity toward sympathetic predominance was reported to be lower in obese than in lean individuals[12] and in insulin-resistant patients,[13] suggesting that chronic hyperinsulinemia may prevent further enhancement of cardiac sympathetic tone during an acute rise in insulin.

In addition, recent data suggest that the incretin hormone glucagon-like peptide 1 (GLP-1) may also play a role in this context. Regarding the effects of GLP-1 on autonomic activity, both the acute and chronic administration of central long-lasting GLP-1 receptor agonist exendin-4 was shown to reduce HF and LF powers of HR variations and to inhibit neurotransmission to cardiac vagal neurons.[14] GLP-1, administered peripherally or centrally, also increases sympathetic activity in rats.[15] Further studies on the effects of GLP-1 on autonomic activity need to be performed in diabetic and obese patients to determine the role of GLP-1 in these populations.

Thus, insulin and GLP-1 are able to induce vagal depression and sympathetic activation (see **Fig. 29-1**). Both hormones may potentially affect BP with effects that might differ depending on the presence of hypertension, cardiac autonomic impairment, and endothelium function.

Vagosympathetic Imbalance and Hemodynamic Changes

Sympathetic activity was found to be greater and baroreflex sensitivity more severely impaired in individuals with obesity and hypertension than in those with either obesity or hypertension alone[16] and similarly for individuals with the metabolic syndrome and hypertension,[17] suggesting that sympathetic overactivity may contribute to hypertension. Vagal impairment and/or sympathetic overactivity may also contribute to resting sinus tachycardia.

At advanced stages of diabetic CAN sympathetic activity is depressed, which may induce orthostatic hypotension (OH).[18] Postprandial hypotension may also occur as a result of meal-induced splanchnic vasodilation while sympathetic response is blunted (**Fig. 29-2**).

EPIDEMIOLOGICAL DATA

Prevalence and Correlates of Cardiovascular Autonomic Neuropathy

In clinical studies including both T1DM and T2DM patients, the prevalence of confirmed CAN (defined by at least two abnormal cardiovascular autonomic reflex test [CART] results) was approximately 20%.[19,20] However, prevalence rates increased with age and diabetes duration (up to 35% in T1DM and 65% in T2DM patients with longstanding diabetes). Glycemic control and the presence of microvascular complications (polyneuropathy, retinopathy, nephropathy) are other correlates of CAN.[19–21] A contributing role of several cardiovascular risk factors (high BP or hypertension, smoking, dyslipidemia, overweight or obesity in T2DM, large waist circumference, high insulin levels in T2DM, and cardiovascular disease) has also been reported. The influence of overweight and obesity is supported by the high prevalence of impaired cardiac vagal activity in nondiabetic obese patients[22] and the finding of an inverse correlation between HR variability and body weight in the general population.[23] This suggests that cardiac autonomic dysfunction precedes the onset of T2DM and might play a role in metabolic disorders.

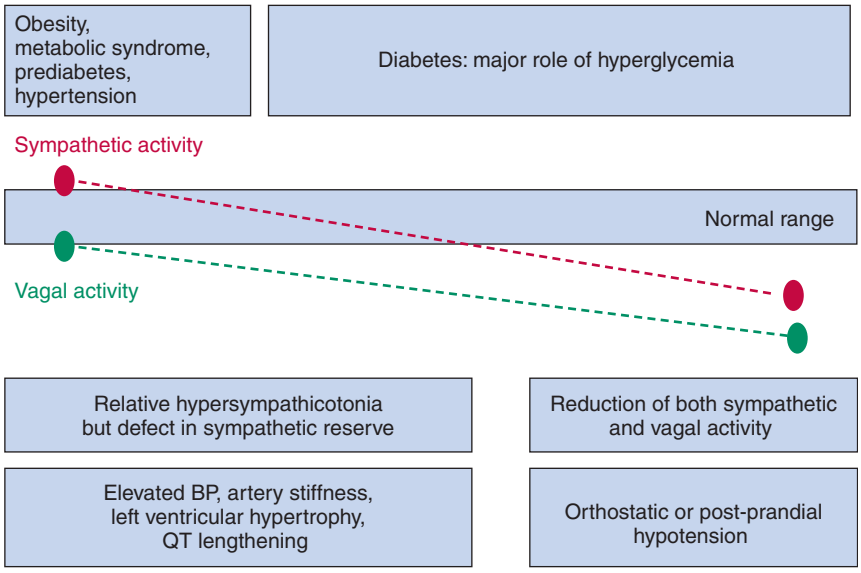


FIGURE 29-2 Changes in vagal and sympathetic activity in the diabetes continuum. BP = Blood pressure.

Cardiovascular Autonomic Neuropathy as a Predictor of Cardiovascular Morbidity and Mortality

CAN is a risk marker for all-cause and cardiac mortality, stroke, coronary events, silent myocardial ischemia (SMI), heart failure, arrhythmia, sudden death, and nephropathy progression.[24] A meta-analysis of 15 longitudinal studies, which included 2900 patients followed for 1 to 16 years, showed that the diagnosis of CAN based on at least two abnormal CART results determined a relative risk of mortality of 3.45 (95% confidence interval 2.66-4.47; $P < 0.001$).[25] Subsequent studies including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[26] confirmed the independent predictive value of CAN for all-cause and cardiovascular mortality (still predictive after adjustment for cardiovascular risk factors). The presence of OH, a clinical manifestation of severe CAN, impaired the prognosis and was associated with a higher mortality risk than the increase in risk associated with vagal cardiac test abnormalities.[25] Prolongation of the QT interval corrected for HR (QTc), which may result from CAN, is also an independent predictor of all-cause and cardiovascular mortality.[27]

CARDIOVASCULAR DISORDERS ASSOCIATED WITH CARDIOVASCULAR AUTONOMIC NEUROPATHY

Several disorders associated with subclinical CAN and subsequent to sympathetic predominance may account for the increase in cardiovascular events (**Fig. 29-3**).

Silent Myocardial Ischemia

SMI may be detected by stress ECG or by stress myocardial scintigraphy or echocardiography. In a meta-analysis of 12 studies including 1468 diabetic patients, SMI was present in 20% of those with CAN compared with 10% of those without CAN, with a prevalence rate ratio of 1.96.[28] The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial, which assessed the role of routine screening for ischemia using nuclear stress testing compared with usual care, showed that in 1123 T2DM patients an abnormal Valsalva maneuver was the strongest determinant of SMI.[29] The lowest quartile of HR response in the lying-to-standing test was associated with an adjusted hazard ratio of 4.33 for cardiac death or nonfatal myocardial infarction over a mean follow-up of 4.8 years.[30] In addition, we reported that CAN enhances the cardiac risk associated with SMI.[31] Thus, CAN testing may be considered a main component of a diabetes-specific risk pattern to identify high-risk patients in whom screening for SMI is more effective,[32] although the efficacy of such a strategy awaits confirmation in a controlled clinical trial.

Hypertension

A defect in vagal activity might contribute to hypertension through a relative sympathetic override. This is supported by a study in rats with ventromedial hypothalamic obesity that exhibited a marked bradycardia and only a mild increase in BP. In these rats heart vagal tone was increased, and adrenal medulla secretion was enhanced probably as a result of hyperinsulinemia. In addition, increased vagal activity was observed, and cardiac responsiveness to beta-agonist stimulation was also increased.[33] This suggests that high vagal activity may be protective against hypertension associated with obesity. In patients with T1DM or T2DM we showed that the prevalence of hypertension increased with CAN severity, which supports the role of CAN contributing to hypertension in diabetic patients.[34] Furthermore, a large majority of the patients with macrovascular complications, retinopathy, or nephropathy exhibited the CAN-plus-hypertension profile, which is consistent with a deleterious effect of CAN on vascular hemodynamics and structure, additive to the effects of hypertension.[34] Similarly, we recently found a relationship between the severity of cardiac autonomic dysfunction and the prevalence of hypertension in nondiabetic obese patients (unpublished data).

Left Ventricular Dysfunction

CAN has been reported to be associated with left ventricular systolic and particularly diastolic dysfunction.[35,36] However, it is difficult to evaluate the independent role of CAN in these disorders and in chronic heart failure, because interstitial myocardial fibrosis and microangiopathic or metabolic changes may also contribute to diabetic myocardial disease and left ventricular dysfunction.

QT Interval Prolongation

QTc prolongation may result from imbalance in cardiac sympathetic innervation but also from metabolic and electrolytic myocardial changes, left ventricular hypertrophy, coronary artery disease, and genetic factors. In a meta-analysis of 17 studies including 4584 diabetic patients, QTc prolongation (corrected QT for HR >441 milliseconds) was a specific (86%) but insensitive (28%) index of CAN.[37] Using 24-hour electrocardiographic recordings, we showed that the day-night modulation of the QT/RR-interval relationship was altered in CAN patients free of coronary artery disease or left ventricular dysfunction or hypertrophy, with a reversed day-night pattern and an increased nocturnal QT-HR dependence.[38]

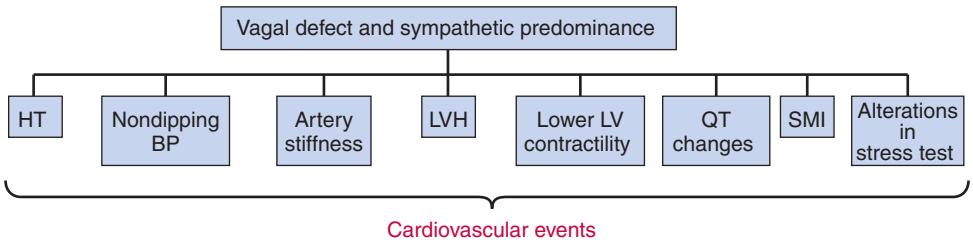


FIGURE 29-3 Cardiovascular disorders induced by CAN. BP = Blood pressure; HT = hypertension; LV = left ventricular; LVH = left ventricular hypertrophy; SMI = silent myocardial infarction.

In T1DM patients, prolonged QTc has been reported to occur frequently during overnight hypoglycemia and to be associated with cardiac rate and rhythm disturbances. Reversible QTc prolongation may be induced by hyperglycemia and by acute hypoglycemia in both healthy and diabetic patients. These findings support an arrhythmic basis for the "dead in bed" syndrome and possibly a provocative role in cardiovascular events of hypoglycemia-induced sympathetic activation.[39] Thus, the presence of CAN may identify diabetic patients more susceptible to the deleterious effects of hypoglycemia, in particular among those with a coronary artery disease. CAN testing may also serve to inform the choice of glycemic control targets according to the patient's risk profile and to balance the advantage of aggressive glucose-lowering treatment versus its risk. Moreover, QTc measurement may be used for cardiovascular risk stratification.[24]

Abnormal Circadian Blood Pressure Pattern

An abnormal circadian BP pattern on ambulatory blood pressure monitoring (ABPM) is associated with CAN. Normal circadian BP changes are characterized by lower levels during the night than during the day. Nondipping and reverse dipping, defined as attenuation or loss of BP and nocturnal fall, respectively, may result from CAN. Several studies linked nondipping to changes in the circadian variation of sympathovagal activity, consisting of a diminished increase in vagal activity and sympathetic predominance during the night.[40,41] Nondipping or reverse dipping was associated with left ventricle hypertrophy[42] and was found to predict the progression of nephropathy independently of 24-hour BP level. Thus ABPM may be useful in patients with CAN to detect disturbance of normal circadian BP variability, to determine risk stratification for cardiovascular mortality and nephropathy progression, and to adjust antihypertensive treatment.

Exercise Intolerance

In diabetic patients with cardiac autonomic neuropathy, exercise capacity and the HR, BP, and cardiac stroke volume responses to exercise are found to be diminished, with a further decrease in exercise capacity and BP response in patients with both vagal neuropathy and OH. The severity of CAN correlates inversely with maximal HR increase during exercise, suggesting CAN contribution to altered exercise tolerance.[43] We also found an impairment of HR recovery after exercise in diabetic patients with CAN but free of SMI. CAN testing offers a useful tool to identify patients with potentially poor exercise performance and to prevent adverse outcomes when patients are introduced to exercise training programs.[24] Thus, CAN testing may be considered before a stress exercise test and also before initiation of a program of vigorous physical activity.[24]

Arterial Stiffness

Using spectral analysis we showed in obese and diabetic hypertensive patients that the low-frequency peak of systolic BP variations in the standing position, which reflects sympathetic activity, correlated significantly with pulse pressure measured in the lying position, suggesting that an increase in arterial stiffness is associated with a higher sympathetic activity.[44] In the Pittsburgh Epidemiology of Diabetes Complications study, CAN function was evaluated in a childhood-onset T1DM population and was associated with increased arterial stiffness measured 18 years later.[45] Some experimental data support the role of a possible protective effect of vagal activity and an aggravating role of sympathetic predominance in arterial stiffness.[46]

DETECTION OF SUBCLINICAL CARDIOVASCULAR AUTONOMIC NEUROPATHY

Detection in Clinical Practice

Standard Tests

Subclinical CAN is a frequent condition that is usually documented with CARTs, the gold standard for clinical autonomic testing. These tests consist of analysis of HR response to deep breathing, lying to standing, and Valsalva maneuver (HR tests), and BP response to standing.[24] HR variations during these tests are indices mainly of parasympathetic function, whereas the presence of OH indicates a sympathetic defect (**Table 29-1**). Knowledge of age-related normal ranges of HR test results is mandatory for accurate analysis of the results (**Fig. 29-4**). These tests are noninvasive, safe, clinically relevant, easy to perform, sensitive, specific, reproducible, and standardized.[24] However, in the absence of data on the potential risk of retinal complications, avoiding the Valsalva maneuver in patients with proliferative retinopathy may be appropriate.[24]

CARTs need to be performed with avoidance of confounding factors. Patients should be requested to avoid strenuous physical exercise in the 24 hours preceding the tests and caffeinated beverages, smoking, and alcohol at least 2 hours before the tests. Testing should be performed at fasting or at least 2 hours after a light meal, and in insulin-treated patients at least 2 hours after short-acting insulin administration, and not during hypoglycemia or marked hyperglycemia. In addition, test results should be interpreted with caution in patients with chronic obstructive pulmonary disease, respiratory failure, obstructive sleep apnea syndrome, or cardiac diseases, in particular heart failure. An appropriate washout of interfering drugs, particularly diuretics, sympatholytic agents, and psychoactive drugs should be considered, and if this is not feasible, then results should be interpreted cautiously.

CARTs need to be performed in a standardized way, with HR variations during the tests being analyzed with use of a

TABLE 29-1 Tests to Detect Subclinical Cardiovascular Autonomic Neuropathy in Clinical Practice or in Clinical Research

SETTING	TESTS
Standard tests in clinical practice	Analysis of HR variations during: · Deep breathing · Lying to standing · Valsalva Assess postural hypotension
In clinical research	· Cardiac vagal baroreflex sensitivity · Frequency domain measures of HR and BP variations · Measurement of muscle or skin sympathetic nerve activity · Plasma catecholamines · Heart sympathetic imaging

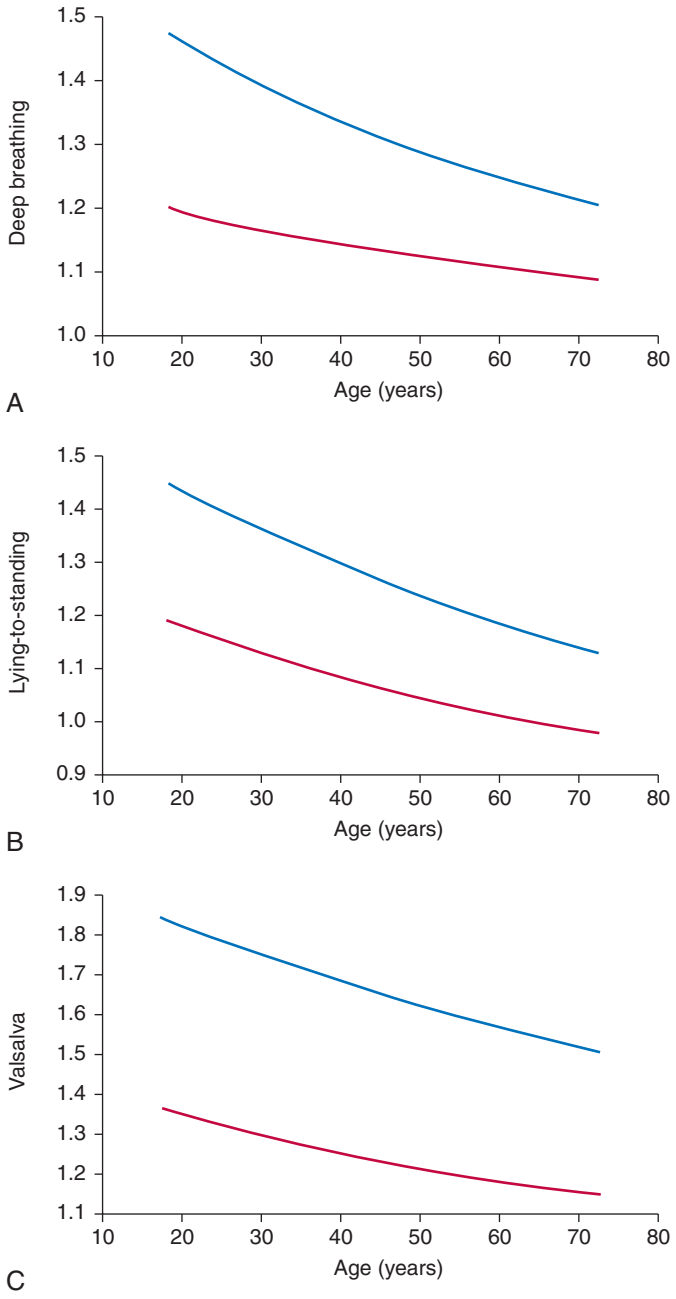


FIGURE 29-4 Influence of age on autonomic HR test results. Correlations (blue line) between RR ratio during the three CAN function tests—**A,** deep breathing; **B,** lying to standing; and **C,** Valsalva—with age in healthy individuals. Results obtained in one patient need to be located on the figures. Results are abnormal if below the 5th percentile line (red line). *(Modified from Valensi P: Comment rechercher une neuropathie autonome cardiaque? In: Coeur et Diabète, Frison Roche Ed, Paris, 1999.)*

simple cardiograph or an electrocardiographic computer system. Briefly, the deep-breathing test consists of six deep respiratory cycles in one minute in the recumbent position; the result is expressed as the mean value for the ratio of maximal RR (interval between two consecutive R waves on the electrocardiogram [ECG]) during breathing out to minimal RR during breathing in at each respiratory cycle. For the lying-to-standing test, the patient is asked to remain lying for 1 minute and then to stand up quickly; the result is expressed as the ratio of the longest RR interval (approximately the 30th beat after standing up) to the shortest RR interval (approximately the 15th beat). The Valsalva test is carried out with the patient seated. He or she is asked to exhale a deep breath to maintain 40 mm Hg pressure for 15 seconds; the Valsalva ratio is calculated by the longest RR interval after breathing out divided by the shortest RR interval while breathing out. OH is defined as a reduction of systolic BP of at least 20 mm Hg or diastolic BP of at least 10 mm Hg within 3 minutes of standing, and a systolic fall in BP of 30 mm Hg in hypertensive patients.[24]

Cardiovascular Autonomic Neuropathy Staging

A definite diagnosis of CAN and CAN staging require more than one HR test and the measurement of BP response to standing. One abnormal cardiovagal test result identifies the condition of possible or early CAN, to be confirmed over time; at least two abnormal cardiovagal test results among the three HR tests are required for a definite or confirmed diagnosis of CAN. The presence of OH in addition to HR test abnormalities identifies severe or advanced CAN (**Fig. 29-5**).[18,24]

Evaluation of Vagosympathetic Activity in Clinical Research

More sophisticated approaches to evaluate CAN may be used in clinical research, including frequency domain measures of HR and BP variations, baroreflex sensitivity, muscle or skin sympathetic nerve activity, plasma catecholamines, and heart sympathetic imaging (see **Table 29-1**).[18,47]

- Frequency-domain indexes can be obtained by spectral analysis of HR variations applied on short (5- to 7-minute) and longer (24-hour) ECG recordings. HF spectral power provides a measure of parasympathetic modulation, whereas LF power evaluates both sympathetic and parasympathetic modulation. The LF power of BP variations provides a measure of sympathetic modulation.
- Cardiac vagal baroreflex sensitivity can be assessed by analysis of HR and BP response to pharmacologic or spontaneous BP perturbations.
- Sympathetic outflow can be measured directly via microelectrodes inserted into a fascicle of a distal sympathetic nerve to the skin or muscle, at rest and in response to various physiologic perturbations.
- Whole-body sympathetic activity is assessed by measuring plasma concentrations of noradrenaline and adrenaline.
- Cardiac sympathetic innervation may be analyzed through scintigraphic studies performed with radiolabelled noradrenaline analogues (iodine-123 [^{123}I]–metaiodobenzylguanidine [MIBG] or carbon-11 [^{11}C]–hydroxyephedrine [HED]).

CLINICAL CONTEXT

Diagnosing Cardiovascular Autonomic Neuropathy in Symptomatic Patients

Symptomatic manifestations of CAN include resting sinus tachycardia, OH, postprandial hypotension, and poor exercise tolerance.

Patients may report palpitations, and tachycardia may be repetitively observed. Emerging evidence on the prognostic value of resting HR has led to the advice in the current hypertension guidelines to measure HR in clinical practice[48] and to use it for cardiovascular risk stratification and as a therapeutic target in high-risk patients.[24]

OH may result from advanced CAN and other factors including drugs and hypovolemia. OH may induce orthostatic symptoms including dizziness, blurred vision, fainting, or pain in the neck or shoulder when standing, and may

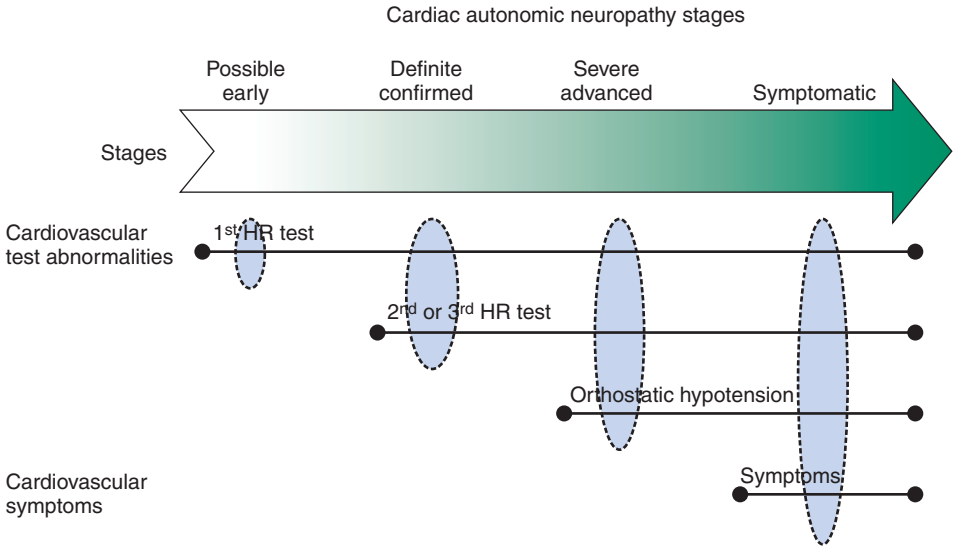


FIGURE 29-5 Staging cardiac autonomic neuropathy (CAN). *(Modified from Spallone V, Ziegler D, Freeman R, et al: on behalf of the Toronto Consensus Panel on Diabetic Neuropathy: Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management,* Diabetes Metab Res Rev, *2011 [Epub ahead of print].)*

induce falls in older adults. Symptoms may be disabling and are often a barrier to an effective antihypertensive treatment.

Postprandial hypotension may induce dizziness and fainting. After excluding any concomitant hypoglycemia, postprandial hypotension may be confirmed by self-measured BP or 24-hour BP monitoring.

The potential cause of CAN in these manifestations or in nondipping or reverse dipping or QT interval prolongation should be confirmed by CARTs.

Screening Asymptomatic Patients

In October 2009 in Toronto (Canada), expert panels were convened to provide updates on the diabetic neuropathies. They suggested screening for CAN at the diagnosis of T2DM and 5 years after the diagnosis of T1DM, particularly in patients at greater risk of CAN because of a history of poor glycemic control, cardiovascular risk factors, diabetic peripheral neuropathy, and macroangiopathic and microangiopathic diabetic complications.[18]

MANAGEMENT OF CARDIOVASCULAR AUTONOMIC NEUROPATHY

Role of Glycemic Control

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized, clinical study designed to determine whether an intensive treatment regimen directed at maintaining blood glucose concentrations as close to normal as possible would affect the appearance or progression of early vascular complications in patients with T1DM. This study showed that intensive insulin treatment reduced the incidence of CAN by 53% compared with conventional therapy. In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a prospective observational follow-up of the DCCT cohort, CAN prevalence and incidence at the 13th to 14th year after DCCT closeout remained significantly lower in the former intensive than in the former conventional group (**Table 29-2**).[49] In the Steno-2 study, which included 160 T2DM patients with microalbuminuria, an intensive multifactorial cardiovascular risk intervention based on tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents reduced the progression or the development of CAN compared with the conventional-therapy group.[50]

TABLE 29-2 Management of Cardiovascular Autonomic Neuropathy

Role of glycemic control	Prevents CAN and its aggravation in patients with T1DM. Avoid hypoglycemia in patients with CAN.
Management of tachycardia	Cardioselective beta blockers can be used to treat resting tachycardia associated with CAN.
Management of OH	Identify other causes of OH—in particular, volume depletion. Avoid drugs exacerbating postural symptoms. Educate patients regarding behavioral strategies, increased fluid and salt intake if not contraindicated. Use elastic garment over the legs and abdomen. If symptoms persist, consider a pharmacologic treatment, weighing its potential risks against its possible benefit.

However, the achievement of tight glycemic control is associated with an increased risk of hypoglycemic events. Through sympathetic activation hypoglycemia may elevate BP, lengthen QT interval with higher risk of arrhythmia, increase cardiac load, and reduce coronary reserve.[39] These effects might be greater in the patients with vagal depression and relative hypersympathicotonia with potential amplification in those treated with insulin (**Fig. 29-6**). Hypoglycemia may also have some delayed deleterious effects on the autonomic nervous system function and affect the responses to future hypoglycemic episodes. Indeed, it has been shown in healthy individuals that a 2-hour hypoglycemic clamp at 2.8 mmol/L depresses sympathetic reactivity measured 16 hours later.[51] Such a prolonged depression of sympathetic reactivity after a hypoglycemic episode may contribute to future hypoglycemia and to the lack of perception of recurrent hypoglycemia. This concept of autonomic failure associated with repeated hypoglycemia is supported by the reversal of

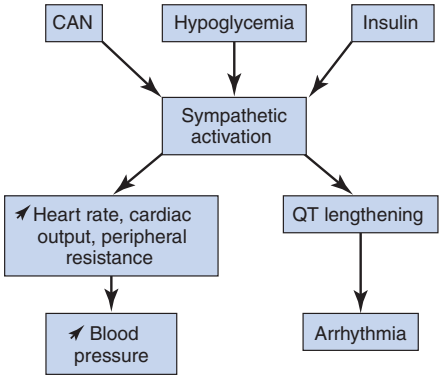


FIGURE 29-6 Cardiovascular changes during hypoglycemic episodes. Potential additional effects of cardiac autonomic neuropathy (CAN) and insulin treatment.

hypoglycemia unawareness and the improvement of the epinephrine response to hypoglycemia after scrupulous avoidance of hypoglycemia for 2 to 3 weeks.[52] Altogether these data should lead to prevention of hypoglycemia in patients with CAN—in particular, those with coronary artery disease.

Management of Tachycardia and Orthostatic Hypotension

An increase in HR variability has been described in diabetic patients taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers, cardioselective beta blockers without intrinsic sympathomimetic activity, digoxin, and verapamil. Cardioselective beta blockers can be used to treat resting tachycardia associated with CAN.

In patients with OH, the first steps are to identify other causes of OH—for example, volume depletion—and avoid drugs that exacerbate postural symptoms, such as psychotropic drugs, diuretics, and alpha-adrenoreceptor antagonists; to educate patients regarding behavioral strategies (e.g., gradual staged movements with postural change, head-up bed position during sleep) and increased fluid and salt intake if not contraindicated; and to prescribe the use of elastic garments over the legs and abdomen. If symptoms persist, a pharmacologic treatment should be considered, weighing its potential risks against its possible benefit (balance between the increase in standing BP and the avoidance of marked supine hypertension). The peripheral selective alpha$_1$-adrenergic agonist midodrine is a first-line drug. Fludrocortisone, erythropoietin (in particular in patients with anemia associated with severe CAN), and acarbose (useful in attenuating postprandial hypotension) are other possible treatments (see **Table 29-2**).

In conclusion, CAN assessment is relevant in clinical practice for diagnosis of asymptomatic forms of CAN, to confirm the cause of CAN in patients with resting tachycardia and orthostatic hypotension, and to explain symptoms (e.g., gastrointestinal or urinary symptoms) suggestive of diabetic autonomic dysfunction. CAN contributes to the increase in cardiovascular risk in patients with diabetes. The detection of CAN may help tailor therapeutic strategies and exercise programs. It may help in the individualized treatment of OH, tachycardia, and nondipping and nocturnal hypertension. In the presence of CAN, drugs with adverse autonomic consequences should be avoided, and drugs with the potential to prolong QT interval should be excluded where possible. CAN assessment is also relevant for tailoring glycemic targets of antidiabetic therapy.

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30 Disparities in Diabetes Risk, Cardiovascular Consequences, and Care

Women, Ethnic Minorities, and the Elderly

Cheryl P. Lynch, Kelly J. Hunt, and Leonard E. Egede

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DISPARITIES IN DIABETES RISK

Type 2 diabetes is a growing problem that closely parallels the obesity epidemic and places a severe burden on health care resources in the United States (see also **Chapter 1**). Diabetes currently affects 25.8 million Americans, 8.3% of the United States population, approximately 95% of whom have type 2 diabetes.[1,2] The lifetime risk of developing type 2 diabetes for individuals born in 2000 in the United States was estimated to be 32.8% in men and 38.5% in women.[3] Diabetes affects all age, sex, ethnic, and racial groups, but disproportionately affects minority populations, with African Americans and Hispanics having a twofold to threefold increased risk of developing diabetes relative to whites.[2,4] Projections indicate that over half of Hispanic women (i.e., 52.5%), almost half of African American women (i.e., 49.0%), and almost one out of every three white women (i.e., 31.2%) will develop diabetes in their lifetime.[3] Projections are slightly lower in men but remain high, with 45.5% of Hispanic men, 40.2% of African American men, and 26.7% of white men projected to develop diabetes during their lifetime.[3]

As the prevalence of diabetes increases, individuals are diagnosed at earlier ages, resulting in greater duration and comorbidity burden and earlier mortality.[3] In African Americans, diabetes diagnosed at age 50 implies living with diabetes for over a quarter of one's life (i.e., average duration, 18.1 years; 10.1 years of life lost), and diagnosis at 30 implies living with diabetes for almost half one's life (i.e., average duration, 28.2 years; 17.1 years of life lost).[3] In Hispanics and whites, diagnosis at age 30 similarly implies living with diabetes for over half one's life (i.e., average duration, 37.7 and 35.3 years, respectively; 14.8 and 13.2 years of life lost, respectively).[3]

From 1980 through 2011, based on information from the National Health Interview Survey (NHIS),[5,6] the prevalence of people with self-reported diagnosed diabetes increased by 167% (from 0.6% to 1.6%) for those aged 0 to 44 years, 118% (from 5.5% to 12.0%) for those aged 45 to 64 years, 140% (9.1% to 21.8%) for those aged 65 to 74 years, and 125% (8.9% to 20.0%) for those aged 75 years and older (**Fig. 30-1**). In general, throughout the time period, the percentage of people with diagnosed diabetes increased among all age groups. In 2011 the percentage of diagnosed diabetes among people aged 65 to 74 (21.8%) was more than 13 times that of people younger than 45 years (1.6%). The NHIS is a health survey of the civilian, noninstitutionalized household population of the United States and has been conducted continuously since 1957 by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC).[5,6] In 2011, 63% of the adult incident cases (i.e., cases diagnosed within the previous year) of diabetes were diagnosed in patients between the ages of 40 and 64 years.[6] About 16% were diagnosed in individuals younger than age 40, and approximately 21% were diagnosed in individuals age 65 or older (**Fig. 30-2**).[6,7]

From 1980 to 1998, the age-adjusted prevalence of self-reported diagnosed diabetes for men and women was similar. However, in 1999 the percentage for men began to increase at a faster rate than the percentage for women. From 1980 to 2011, the age-adjusted percentage of diagnosed diabetes increased from 2.7% to 6.9% for men and from 2.9% to 5.9% for women (**Fig. 30-3**).

Using data from the NHIS, the incidence of diagnosed diabetes in the United States was estimated from 1997 to 2011 and during this time period the age-adjusted incidence of diagnosed diabetes increased among all racial and ethnic groups and was higher in African Americans and Hispanics than in whites. The age-adjusted incidence of diagnosed diabetes was 12.4/1000 in African Americans, 11.1/1000 in Hispanics, and 7.0/1000 in whites (**Fig. 30-4**).

DISPARITIES IN CARDIOVASCULAR CONSEQUENCES

Diabetes Comorbidities in Racial and Ethnic Minorities

Diabetes is the seventh leading cause of death in the United States. Previous studies report up to a threefold increase in mortality risk associated with diabetes.[8–13] In the Framingham Heart Study, which included white men and women living in Framingham from 1950 through 1975, the age- and sex-adjusted hazard ratio (HR) associated with diabetes

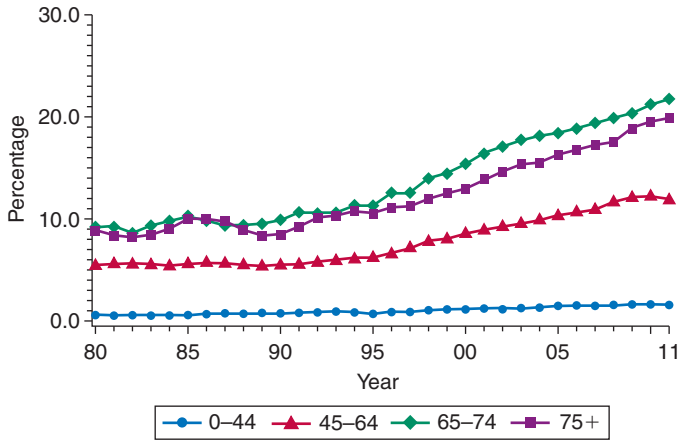


FIGURE 30-1 Percentage of civilian, noninstitutionalized population with diagnosed diabetes, by age, United States, 1980-2011. *(Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Percentage of civilian, noninstitutionalized population with self-reported physician diagnosed diabetes, by age, United States, 1980-2011. Data from the National Health Interview Survey, National Center for Health Statistics, Division of Health Interview Statistics. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm. Accessed on 5/11/2014.)*

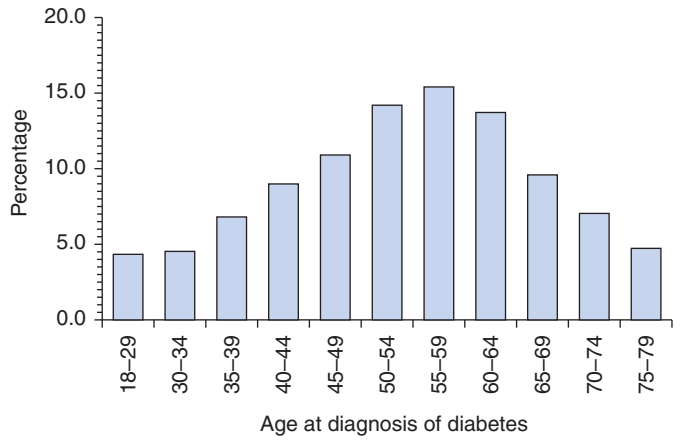


FIGURE 30-2 Distribution of age at diagnosis of diabetes among adult incident cases in patients aged 18 to 79 years, United States, 2008. *(Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Distribution of age at diagnosis of diabetes among adult incident cases in patients aged 18 to 79 years, United States, 2011. Data from the National Health Interview Survey, National Center for Health Statistics, Division of Health Interview Statistics. Available at: http://www.cdc.gov/diabetes/statistics/age/fig1.htm. Accessed on 5/11/2014.)*

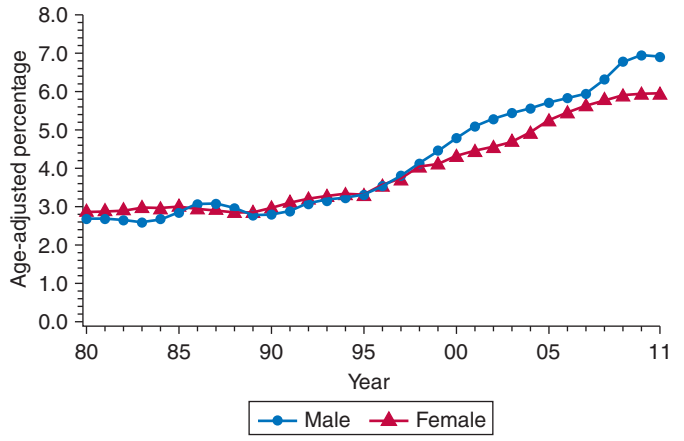


FIGURE 30-3 Age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes, by sex, United States, 1980-2010. *(Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes, by sex, United States, 1980-2011. Data from the National Health Interview Survey, National Center for Health Statistics, Division of Health Interview Statistics. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figbysex.htm. Accessed on 5/11/2014.)*

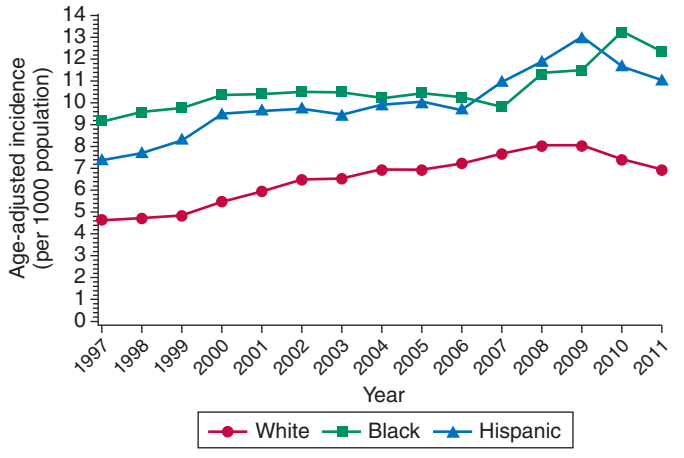


FIGURE 30-4 Age-adjusted incidence of self-reported diagnosed diabetes per 1000 population aged 18 to 79 years, by race or ethnicity, United States, 1997-2010. *(Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Age-adjusted incidence of self-reported diagnosed diabetes per 1000 population aged 18 to 79 years, by race or ethnicity, United States, 1997-2011. Data from the National Health Interview Survey, National Center for Health Statistics, Division of Health Interview Statistics. Available at: http://www.cdc.gov/diabetes/statistics/incidence/fig6.htm. Accessed on 5/11/2014.)*

for all-cause mortality was 2.44 (95% confidence interval [CI] 1.99-2.98), whereas the respective HR for the time period 1976 to 2001 was 1.95 (95% CI 1.63-2.33).[12] The age- and sex-adjusted HR for diabetes in non-Hispanic whites in the San Antonio Heart Study, a cohort study of non-Hispanic whites and Mexican Americans living in San Antonio, Texas, is 1.88 (95% CI 1.28-2.77) and is comparable to results from the second time period of the Framingham Heart Study.[14] In contrast, in U.S.-born Mexican Americans in the San Antonio Heart Study, there was a threefold increased risk of mortality associated with diabetes.[14] Unexpectedly, in the San Antonio Heart Study, adjusting for cardiovascular risk factors altered associations only slightly, indicating that the increased mortality risk associated with diabetes in U.S.-born Mexican Americans is independent of cardiovascular risk factors at least to the extent that they were adjusted for.

In the United States, diabetes is a major cause of heart disease and stroke as well as the leading cause of kidney failure, nontraumatic lower-limb amputations, and development of blindness in adults (see also **Chapters 7**, **11**, **27**, and **28**). The incidence of coronary disease is twofold to fivefold higher in those with diabetes relative to those without diabetes[9,15–19]; the risk of renal failure is twofold higher, the risk of blindness is 20-fold higher, and the risk of lower-extremity amputation is 40-fold higher in those with diabetes relative to those without diabetes.[20,21] At the Veterans Health Administration (VHA), diabetes accounts for approximately 50% of cerebrovascular events, 40% of patients with end-stage renal disease receiving dialysis, and over 70% of amputations.[22]

Relative to whites, African Americans with diabetes are at higher risk of complications typically related to hypertension

including end stage renal disease, lower-extremity amputation, blindness, and stroke. This is not surprising, given that it is well established that hypertension is more common and less well controlled in African Americans than whites.[23–25] In studies conducted using the Third National Health and Nutrition Examination Survey (NHANES III), the presence of any diabetic retinopathy lesion was 46% higher in African Americans than in whites, with African Americans also more likely to have moderate or severe retinopathy when compared with whites.[26] End-stage renal disease is a growing problem in the United States, with diabetes accounting for approximately 45% of new patients requiring renal replacement therapy and the incidence of end-stage renal disease increasing more than 80% between 1993 and 2003.[27] Disparities in end-stage renal disease are vast, with incidence rates of 976/million in African Americans and 277/million in whites in 2009, a 3.5-fold higher incidence in African Americans than whites.[27,28] Between 1980 and 2008, the age-adjusted incidence of treatment (i.e., dialysis or transplant) for end-stage renal disease in individuals with diabetes varied by race and gender groups (**Fig. 30-5**).[29] Among individuals with diabetes, the incidence of end-stage renal disease was highest in African American men and lowest in white women. In whites and African Americans with diabetes, the incidence of end-stage renal disease increased in the 1980s, but started to decrease in the 1990s.[29] This can be explained by the increasing incidence of end-stage renal disease in the U.S. population because, although in recent years a lower percentage of individuals with diabetes have developed incident end-stage renal disease, the total number of individuals with diabetes and end-stage renal disease continues to increase. In a study conducted within the Veterans Administration, in which differences in socioeconomic status (SES) and access to care are limited, African Americans with diabetes were also more likely to have nephropathy and end-stage renal disease than whites with diabetes after adjustment for age, sex, and economic status.[31]

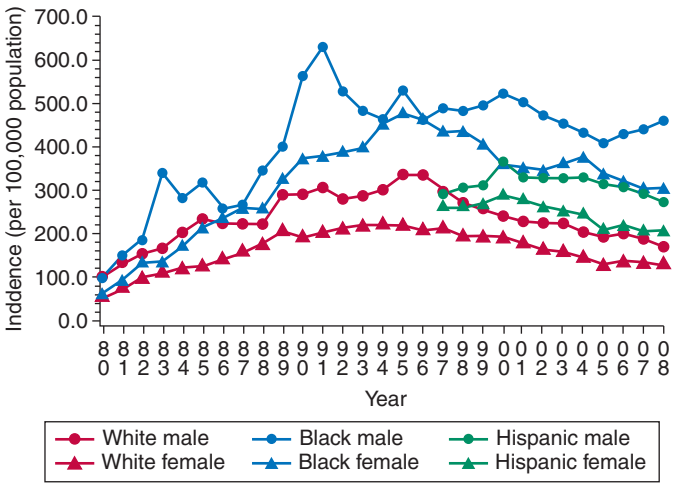


FIGURE 30-5 Age-adjusted incidence of end-stage renal disease related to diabetes mellitus (ESRD-DM) per 100,000 diabetic population, by race, ethnicity, and sex, United States, 1980-2008. *(Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Age-adjusted incidence of end-stage renal disease related to diabetes mellitus (ESRD-DM) per 100,000 diabetic population, by race, ethnicity, and sex, United States, 1980-2008. Data from the United States Renal Data System funded by National Institutes of Health; National Health Interview Survey, National Center for Health Statistics. Available at: http://www.cdc.gov/diabetes/statistics/esrd/fig5.htm. Accessed on 11/14/2013.)*

Similar to end-stage renal disease, the incidence and prevalence of lower-extremity amputation is higher in African Americans with diabetes than in whites with diabetes. Using age-adjusted hospital discharge rates for nontraumatic lower-extremity amputation, in whites the rates declined from 6.2/1000 individuals with diabetes in 1988 to 2.3/1000 individuals with diabetes in 2009.[32] During the same time period, rates also declined in African Americans, from 6.7/1000 to 4.5/1000 individuals with diabetes, but remained almost twice as high when compared with whites in 2009. In a study conducted within the Veteran Administration, African Americans with diabetes were more likely to undergo a lower-extremity amputation than whites with diabetes.[33]

In contrast to microvascular disease, macrovascular complications, including myocardial infarction and cardiovascular mortality, which are typically related to dyslipidemia, seem to have similar or even lower rates in African Americans with diabetes than whites with diabetes.[34] The similar or even lower rates of heart disease in African Americans may be a result of their distinct but favorable lipid profiles when compared with whites.[35–37]

Relative to whites, Mexican Americans with diabetes are at higher risk of microvascular as well as macrovascular disease.[13,38] In NHANES III, the presence of any diabetic retinopathy lesion was 84% higher in Mexican Americans than whites, with Mexican Americans also more likely to have moderate or severe retinopathy when compared with whites.[26] Rates of end-stage renal disease are also higher in Hispanics than whites.[29,30] In 1997, when the United States Renal Data System began collecting information on ethnicity, the age-adjusted incidences of end-stage renal disease were 293.2/100,000 men and 264.1/100,000 women with diabetes (see **Fig. 30-5**).[29,30] In 2008, rates had declined to 271.8/100,000 men and 205.8/100,000 women with diabetes. However, in contrast to African Americans, Mexican Americans with diabetes also appear to have increased risk of macrovascular disease relative to whites, although there remains some controversy.[29,30] In a study of 827 diabetic San Antonio Heart Study participants, age- and sex-adjusted HRs indicated that U.S.-born Mexican Americans with diabetes had a 70% greater risk of all-cause mortality and a 60% greater risk of cardiovascular mortality than non-Hispanic whites with diabetes.[13] In the San Luis Valley Diabetes Study, of nondiabetic participants, Mexican Americans and whites were at equal risk of incident coronary heart disease (CHD), whereas of diabetic participants, whites were at a higher risk than Mexican Americans of incident CHD.[39] In contrast, a community-based surveillance project, the Corpus Christi Heart Project, reported a higher incidence of hospitalized CHD among Mexican Americans than whites,[40] a higher CHD fatality rate among Mexican Americans than non-Hispanic whites,[41,42] and higher community-wide CHD mortality (both in and out of hospital) in Mexican Americans than non-Hispanic whites.[43]

Factors potentially associated with racial or ethnic differences in comorbidity burden include biologic differences in diabetes severity triggered by genetic or environmental factors as well as differences in health care access, treatment practices, and ongoing prevention efforts. Unfortunately, available markers of biologic differences in disease severity including medication use, insulin use, fasting glucose levels, and duration of clinically recognized diabetes are intrinsically tied to health care use and treatment. Increased access

to care and disease awareness likely result in a shorter time to recognition and treatment of disease, a higher prevalence of recognized diabetes, a lower prevalence of unrecognized diabetes, and improved outcomes. Duration of diagnosed and duration of undiagnosed diabetes (i.e., time to recognition and treatment) may also be affecting severity and outcomes differently across populations.

Diabetes Comorbidities in Women

A large number of studies and at least three meta-analyses have examined whether diabetes reduces the sex difference in CHD mortality.[44–46] Reports from two of the three meta-analyses indicate that the impact of diabetes on the risk of CHD death is greater in women than in men and that standard cardiovascular disease (CVD) risk factors do not fully account for the sex difference,[44,46] whereas the third meta-analysis found that elevated levels of the standard CVD risk factors (i.e., age, hypertension, total cholesterol, and smoking) are responsible for the excess relative risk of CHD mortality in women with diabetes versus men with diabetes.[45] Sex-specific elevations in CVD risk factors (established or novel), sex-specific interactions among CVD risk factors, or sex-specific increased substrate susceptibility may all operate to reduce the sex difference in CHD mortality among individuals with diabetes. If differences in CVD risk factor levels (established or novel) account for all or part of the attenuation of the CHD mortality sex difference in individuals with diabetes, then relative to men, women with diabetes must have higher CVD risk factor levels. This could be explained if diabetes had a more adverse effect on CVD risk factor levels (established or novel) in women than in men, or if diabetes and CVD shared a common antecedent that affected men and women differently. Elevated CVD risk factors in prediabetic individuals,[47–51] elevated CVD risk before a clinical diagnosis of diabetes in the Nurses' Health Study,[48] and elevated carotid artery intima-media thickness in prediabetic individuals in the Mexico City study[52] each suggest an atherogenic state before the onset of clinical diabetes that is consistent with a common cause underlying diabetes and CVD. Furthermore, the metabolic syndrome, recognized as a cluster of CVD risk factors that frequently coincides with insulin resistance and hyperglycemia,[53,54] may be an early manifestation of the common cause underlying diabetes and CHD.

Obesity, specifically increased central adiposity, affects men and women differently and is distributed differently between men and women with and without diabetes. In the Strong Heart Study, differences in waist-to-hip ratio and waist circumference between diabetic and nondiabetic individuals were greater in women than men.[55] Studies also indicate that adverse lipoprotein changes associated with diabetes affect women and men differently.[56–62] In the San Antonio Heart Study, diabetes in Mexican American women was associated with a greater increase in low-density lipoprotein cholesterol (LDL-C) and a greater decrease in high-density lipoprotein cholesterol (HDL-C) levels than in Mexican American men.[61] Adverse lipoprotein changes reported in other studies include greater decreases in HDL-C, apolipoprotein (apo) A-I, and LDL particle size and greater increases in LDL-C and apo B in diabetic women than in diabetic men.[56–62] These lipoprotein changes may be one explanation for the reduced sex difference in CHD mortality among individuals with diabetes.

Disparities in Access to Care

Disparity in access to care is a central issue often directly affected by patients, providers, and the health care system. Access to health care is defined by the Institute of Medicine as having "the timely use of personal health services to achieve the best health outcomes".[63] It requires entry into the health care system, receipt of needed services at health care sites, and development of a relationship of mutual communication and trust with providers who meet the needs of individual patients. The trend of disparities in access to care factors is presented annually by the Agency for Healthcare Research and Quality (AHRQ) in the National Healthcare Disparities report[64] demonstrating issues with basic health care services. An approach to addressing issues in access to cardiovascular care was introduced by an ad hoc task force of the American College of Cardiology in the early 1990s, which reported and provided recommendations in a series of conference reports that presented the current state of care and recommendations for change or improvement (1992 and 1993). This work culminated in a formal policy statement on access to cardiovascular care[65] that supported the "development of an organized system of health care for the underserved," access to "a basic set of essential, clinically appropriate cardiovascular services," and research to explain "differences in utilization of health care procedures in certain populations." Such efforts stimulated a multitude of studies to report on underlying issues regarding differences in the prevention and management of cardiovascular health and use and quality of cardiovascular services. However, studies examining trends in access to cardiovascular care are limited, and even fewer studies attempt to explain disparities in access to cardiovascular care. No formal reporting method exists to reveal the trends in disparities in access to cardiovascular care, particularly in high-risk groups such as patients with preexisting CVD, diabetes, hypertension, hyperlipidemia, and chronic kidney disease.

Despite understanding that access to care is a major barrier to the receipt and use of care services, and that disparities exist with regard to race and ethnicity, SES, provider behavior and practice, and organizational factors, many of the existing disparities remain unexplained.[66] Data from the National Healthcare Disparities Report[64] indicate that there has been no change in disparities between rates of health insurance coverage for ethnic minorities versus non-Hispanic whites (<70% vs. 83%), except in African Americans, for whom insurance coverage is now at 81%. It will be interesting to see how the Affordable Care Act impacts disparities in health and health care with expansion of insurance coverage and reduction in cost-sharing for preventive services. One recent study suggests that the most important contributing factors to the growing disparities between Hispanics and whites are health insurance, education, and income differences.[67] Such disparities in access-related factors are further amplified with loss of employment and periods of uninsurance across all population subgroups. Currently, access to care specific to cardiovascular health is largely limited by racial or ethnic and socioeconomic differences for heart disease and hypertension, congestive heart failure, diabetes, and cardiac procedures.[68]

Pincus and colleagues summarized several studies demonstrating persistent and widened disparities in health according to SES as evidence for the limitations in access to care.[69] For example, in the United States, lack of a high school diploma was a greater risk factor than biologic factors



for development of many diseases, an association only partly explained by age, ethnicity, sex or smoking status. One study of 17,530 employed London civil servants with universal access to the National Health Service showed that job classification, as a measure of SES, was a better predictor of cardiovascular death over 7 years than cholesterol level, blood pressure, and smoking combined. Disparities in health according to SES widened between 1970 and 1980 in the United States and in the United Kingdom, despite universal access. Finally, level of formal education predicted cardiovascular mortality better than random assignment to active drug or placebo over 3 years in a clinical trial that provided optimal access to care.[69] Although Canada has universal health coverage, a study that examined the relationship between access to care and 1-year mortality among patients hospitalized with acute myocardial infarction in the Ontario Myocardial Infarction Database showed that Ontario residents living in lower-income areas had reduced access to invasive procedures and higher mortality rates compared with residents of wealthier neighborhoods.[70]

In the United States, the U.S. Department of Veterans Affairs (VA) health care system is a universal access system for military veterans, yet several studies have clearly demonstrated disparities in cardiovascular prevention and management among veterans with diabetes.[71–74] One study showed that African American veterans with diabetes were 0.72 times less likely to receive lipid-lowering medications than their white counterparts[71] and less likely (40.9% versus 56.9%, respectively) to meet guideline-specific goals for LDL-C (<100 mg/dL).[75] A large cohort study examining control of hyperglycemia among insulin-treated veterans with type 2 diabetes showed poorer glycemic control and less intensive insulin treatment in African Americans compared with whites.[72] However, no differences in control of other CVD risk factors were found. Similar ethnic differences in glycemic control[76] and in blood pressure control[77] over time have been demonstrated in longitudinal studies. One longitudinal study of multiple cardiovascular risk factor control among ethnic minority veterans with diabetes showed that non-Hispanic blacks had a twofold risk of poor control and Hispanics had a 48% higher likelihood of poor control compared with non-Hispanic whites.[78] Such disparities in a health care system that provides a universal level of benefit for its members may reflect differences in treatment intensity, provider behaviors (prescribing patterns), and/or patient behaviors (medication adherence) or preferences.[72]

The collective evidence from these studies strongly suggests that equal access to care does not necessarily translate into equity in clinical outcomes. True equity is achieved when there is equity in access, usage, and outcomes.[79] A number of factors can influence access to cardiovascular services, such as geographic distance, economic barriers, and cultural variables.[80] Access can be further conceptualized to include overall access, contact access, and appointment access.[81] However, access is tightly linked with SES. In addition, SES is often correlated with race and ethnicity through key environmental variables that affect CVD outcomes, such as stress from residence in crime-prone communities, substandard housing, exposure to toxic waste sites, density of fast-food restaurants, limited transportation, and limited educational opportunities. Therefore, studies on disparities in access to care for CVD risk and outcomes need to account for SES.

Sex Disparities in Access to Care

Data on cardiovascular health in women continue to demonstrate that CVD remains a leading cause of death, although CVD-related mortality rates have been declining over time.[82] Sex differences have also been demonstrated in clinical outcomes for CVD. A cross-sectional analysis of 44,893 patients with type 2 diabetes (51% women) showed that women with CVD were less likely to have control of important modifiable risk factors (systolic blood pressure [SBP], LDL-C, and hemoglobin A1c [HbA1c]) and less likely to receive intensive lipid-lowering treatment.[83] Similarly, women without CVD were less likely than men to have lipids controlled, with no differences in SBP or HbA1c control. Such treatment differences can well be attributed to different access to or use of care. A meta-analysis identified 37 studies of type 2 diabetes and fatal CHD among a total of 447,064 patients. Whereas CHD fatality rates were higher in patients with diabetes than in those without (5.4% versus 1.6%), the overall summary relative risk for fatal CHD in patients with diabetes compared with no diabetes was significantly greater among women (3.50, 95% CI 2.70-4.53) than it was among men (2.06, 95% CI 1.81-2.34). This excess CHD risk was attributed to patient and provider factors, with more adverse CVD risk profiles among women with diabetes and possible disparities in treatment that favor men.[84] Excess CHD risk in women has also been attributed to different treatment of CVD risk factors. Studies demonstrate a heavier burden of traditional risk factors and a greater effect of blood pressure and atherogenic dyslipidemia in women with diabetes.[85] Studies have also found greater prescribing of statins (45% versus 35%)[86] and lipid-lowering therapy to achieve recommended LDL-C levels[87] in men compared with women with diabetes.

Studies have shown that women with CVD are screened and treated less aggressively than men and are less likely to undergo cardiac procedures. From a national sample of commercial health plans, women with diabetes had a 19% lower odds (95% CI 0.76-0.86) and women with a history of CVD had a 28% lower odds (0.64-0.82) of achieving the LDL-C goal of below 100 mg/dL. However, women performed better than men with blood pressure control (Odds ratio [OR] 1.12; 95% CI 1.02-1.21). Despite similar access to care, sex disparities were shown in the management and outcomes of CVD among this cohort of privately insured patients. Overall, poor performance in LDL control was seen in both men and women. This suggests that less intensive treatment of cholesterol occurred in the cohort of women.[88] Therefore the differences in patterns of care demonstrate the need for interventions tailored to address sex disparities.

Although awareness among women of their risk for CVD has improved, disparities in knowledge persist.[89] It is particularly alarming when data suggest that only 57% of women will seek emergency care for symptoms suggestive of a heart attack.[89] The lack of priority in addressing cardiovascular health is supported by findings that middle-aged women with diabetes or cardiovascular conditions were more likely to report delays in care (85% to 111% higher adjusted odds among diabetes patients, 56% to 84% higher adjusted odds among cardiovascular patients; all $P<0.01$) than men.[90]

Ethnic Disparities in Access to Care

The latest CDC report[82] indicates that non-Hispanic blacks continue to have the highest age-adjusted prevalence rates

of diagnosed diabetes (12.6%) among all racial and ethnic groups, and Puerto Ricans had the absolute highest rate (13.8%) among all Hispanics. From 1997 to 2011, the age-adjusted percentage of people with diabetes aged 35 years and older reporting heart disease or stroke was lowest among Hispanics compared with whites or African Americans. In a systematic review of studies on cardiovascular health disparities, most were descriptive in nature with the vast majority of evidence being presented for African American populations.[91] Disparities in access to care can include different provider practice patterns, lack of availability of insurance, and membership in restrictive health plans, as well as other factors that can differently affect the care of certain patient groups.[92] For example, disparities may occur among racial-ethnic groups as a result of observed patient characteristics (e.g., income, language fluency, and health status) and unobserved heterogeneity (e.g., discrimination, attitudes, and cultural differences even among individuals within the same racial-ethnic group).[92,93] To dampen the impact of such issues, recently implemented ACA provisions broaden access to health care services and will increase workforce diversity as a means of improving observed disparities. In summary, a range of system-related and patient-related factors can contribute to racial and ethnic disparities in access to care.

The higher risk of fatal CHD among blacks compared with whites was associated with CVD risk factor burden.[94] When other risk factors are held constant, ethnic minority individuals are at higher risk of CVD mortality at younger ages than non-Hispanic whites.[95] In a study of low-income patients with diabetes, all-cause mortality risk was higher for both African Americans with diabetes (HR 1.84; 95% CI 1.71-1.99) and whites with diabetes (HR 1.80; 95% CI 1.58-2.04) versus those without diabetes. However, among those with diabetes, mortality was lower among African Americans than whites (HR 0.78; 95% CI 0.69-0.87). Mortality risk increased with duration of diabetes, with insulin therapy, and with a history of CVD, hypertension, and stroke. Despite a lower baseline prevalence of CVD, the HRs associated with these multiple risk factors tended to be similar by sex and race with the exception of a higher impact of prevalent CVD on mortality among African Americans. With similarly low SES and access to health care, strong and generally similar predictors of mortality were identified for African Americans and whites with diabetes, with African Americans at a moderately but significantly lower mortality risk.[96]

Whether factors related to health care access can further explain racial disparities in CVD have not been thoroughly examined. The Health, Aging, and Body Composition (Health ABC) Study is a longitudinal study of 3075 well-functioning older adults aged 70 to 79. One Health ABC study examined racial and health care (i.e., health insurance and access to care) associations with CVD indicators (i.e., hypertension, low ankle-arm index, and left ventricular hypertrophy) and found that older African Americans had significantly worse health care compared with white adults. Overall, health care only slightly reduced the significant association between African American ethnicity and risk for CVD, whereas race remained strongly associated with CVD after adjustment for demographics, SES, body mass index, and comorbidity.[97] However, this study may have been limited in demonstrating significant differences, given that all participants had Medicare and access to a regular source of care and that selection bias may have excluded a sicker cohort of individuals. Although studies continue to describe disparities in CVD outcomes and examine underlying reasons for these associations, research on disparities in access to and quality of cardiovascular care, patient- and provider-level characteristics, and the interaction among these factors is needed to provide a more comprehensive understanding of disparities in CVD outcomes.

Studies that address cardiovascular health disparities and access to cardiovascular care in Hispanic, Asian, and Native American populations with diabetes are relatively scarce. In more recent studies among U.S. Hispanic adults of diverse backgrounds, a sizeable proportion of men and women had adverse major risk factors. The prevalence of adverse CVD risk profiles was higher among participants with Puerto Rican background, lower SES, and higher levels of acculturation.[98] In a cross-sectional survey of 211 Latinos (predominantly Puerto Ricans) with type 2 diabetes, higher food insecurity score was a risk factor for experiencing enabling factor (OR 1.46; 95% CI 1.17-1.82), medication access (OR 1.26; 95 CI% 1.06-1.50), and forgetfulness (OR 1.22; 95 CI% 1.04-1.43) barriers.[99] Higher diabetes management self-efficacy was protective against all barriers. Evidence for CVD risk with early-stage disease demonstrates that cardiovascular risk estimates from prehypertension have ranged from no increased cardiovascular mortality, after adjustment for the presence of any CVD risk factor, in NHANES[100] to an 80% increase in CVD risk with prehypertension to a 270% increase with coexisting prehypertension and diabetes among American Indians in the Strong Heart Study.[101]

Age-Related Disparities in Access to Care

Both the quality and quantity of access to health care may be associated with better health through health insurance.[102] Therefore in older adults, Medicare coverage among those who are 65 years of age and older may improve access and outcomes. However, whereas traditional Medicare insurance afforded older adults near universal coverage, current Medicare packages provide more variable access to health care that is dependent on the purchase of supplemental insurance coverage through Medicare or private companies and selection of a regular source of health care. Invariably, access to cardiovascular care is affected by the level of reimbursement for packaged health care services, such as that offered by managed care plans, for older adults. This is supported by findings from a study comparing equity of care according to the Healthcare Effectiveness Data and Information Set (HEDIS) between the VA and Medicare Advantage (a for-profit managed care plan), showing that the VA outperformed Medicare Advantage health plans on widely used clinical performance indicators for diabetes and cardiovascular care among enrollees aged 65 years or older.[103] Further research is needed to understand the role of health care access in racial and ethnic disparities in heart disease among older adults.

Older adults represent a population that can have increased difficulty with access to care. The aging population is faced with multiple coexisting chronic conditions, called multimorbidity. More than 50% of older adults have three or more chronic diseases.[104,105] Despite their eligibility for Medicare at age 65 many of them exist on fixed incomes. Independently living elderly in a lower income bracket creates a barrier for paying premiums for supplemental insurance, affording the copays for multiple primary and

specialty care visits, obtaining durable medical equipment, and bearing the burden of medication costs particularly when Medicare Part D (for prescription coverage) reaches the gap where less coverage is provided. This type of "disparity of aging" prompted development of models of comprehensive care for the elderly that demonstrate improved access to and quality of care[106] such as the Geriatric Resources for Assessment and Care of Elders (GRACE) model, Guided Care, and the Program of All-inclusive Care for the Elderly (PACE).

When examining the pattern of multimorbidity hypertension and diabetes are amongst common clusters of comorbid conditions in the elderly.[107–109] Using diabetes as an example of the burden of health disparities, recent estimates show that diabetes is most prevalent among older adults (65 years and older) at nearly 27%.[110] While several demographic changes are occurring in the US population, one of the most impactful is the proportion of older adults projected to account for a larger segment of the population by year 2050. If current increases in the incidence rate of diabetes continues among adults 65 years of age and older (see **Fig. 30-1**), diabetes cases can be expected to affect one in every two older adults.[111] With the recent implementation of Patient Protection and Affordable Care Act (PPACA) initiatives that address elimination of cost sharing for preventive services and reduced cost sharing for prescription drug benefit, greater availability and access to alternative models of care for the elderly is a distinct possibility. Consequently, health care disparities can be alleviated partly through more efficient and effective complex care that improve health outcomes, functional status, and quality of life among the elderly.

IDENTIFICATION, SCREENING, AND PREVENTION IN HIGH-RISK GROUPS: PRE-DIABETES

Diabetes has an asymptomatic preclinical phase; hence, in the absence of routine screening a significant proportion of individuals with diabetes remain undiagnosed. In a publication using NHANES data from 2005 and 2006, based on fasting plasma glucose as well as 2-hour plasma glucose from an oral glucose tolerance test, it was estimated that in the U.S. adult population aged 20 years or older, the prevalence of undiagnosed diabetes was 5.1%.[112] This translates to a prevalence of undiagnosed diabetes among those with diabetes of 39.7%.[112] Using the American Diabetes Association recently endorsed HbA1c cut point of 6.5% or greater as diagnostic of diabetes, estimates for undiagnosed diabetes were slightly lower at 2.1% in 1988 to 1994, 1.6% in 1999 to 2002, and 1.8% in 2003 to 2006 in the U.S. adult population aged 20 years or older.[113] These values translated to a prevalence of undiagnosed diabetes among those with diabetes of 28.9% in 1988 to 1994, of 20.6% in 1999 to 2002, and of 21.5% in 2003 to 2006.[64] Hence, with fasting and 2-hour plasma glucose used to diagnose diabetes in 2005 and 2006, roughly two fifths of all cases of diabetes were undiagnosed in the U.S. adult population aged 20 years or older.[112] When HbA1c was used to diagnose diabetes in 2003 to 2006, roughly one fifth of all cases of diabetes were undiagnosed.[113]

Expanding the time period to a 10-year window from 1999 through 2008 and defining diabetes based on HbA1c of 6.5% or greater, based on NHANES data in adults aged 20 years or older, the overall prevalence of undiagnosed diabetes was 1.5% (95% CI 1.2-1.8) in whites, 3.1% (95% CI 2.6-3.5) in African Americans, and 2.7% (95% CI 2.1-3.3) in Mexican Americans, whereas the prevalence of diagnosed diabetes was 6.7% (95% CI 6.0-7.3) in whites, 11.3% (95% CI 10.3-12.3) in African Americans, and 7.6% (95% CI 6.8-8.4) in Mexican Americans.[65] Hence, undiagnosed diabetes accounted for 18.5% (95% CI 15.4-21.5), 21.3% (95% CI 18.1-24.6), and 26.0% (95% CI 21.5-30.4) of diabetes in whites, African Americans, and Mexican Americans, respectively.[114] The prevalence of undiagnosed diabetes in the general population increases with age, is higher in men than in women, and is higher in African Americans and Mexican Americans than in whites.[2,112–115]

Based on NHANES data in adults aged 20 years or older from 1999 through 2008, in individuals with undiagnosed diabetes, Mexican Americans were the youngest at 49.1 years, followed by African Americans at 56.5 years and whites at 60.7 years.[114] Mexican Americans and whites were more likely to be male than female—57.5% and 62.4% male, respectively—whereas only 38.1% of African Americans were male.[114] Mexican and African Americans were less likely to have graduated from high school and were more likely to have a low household income than whites.[114] In this study the authors report that in a population representative of individuals in the United States with undiagnosed diabetes, cardiometabolic risk factor levels were high across racial and ethnic groups, but African and Mexican Americans had poorer cardiometabolic risk factor control than whites.[114]

In a recent retrospective cohort study conducted among 1456 African American and 2624 white veterans with recently diagnosed diabetes who were receiving consistent primary care at VHA facilities, the authors reported that at the time of diagnosis of diabetes and at the time of initiation of glucose-lowering medication, glucose and HbA1c levels were higher in African Americans than in whites.[116] Specifically, at the time of diabetes diagnosis, average HbA1c levels were 7.8% in African Americans, but only 7.1% in whites (with similar results for glucose: 154 versus 148 mg/dL). At the time of initiation of glucose-lowering medication, average HbA1c levels were 8.5% in African Americans, but only 7.8% in whites (with similar results for glucose: 176 versus 169 mg/dL).[116]

Several studies have examined chronic complications of diabetes and the economic cost before the onset of clinical diabetes. Studies of chronic complications of diabetes indicate that cardiovascular risk factor levels,[47,49–51,117] atherosclerosis (as measured by carotid artery intima-media thickness),[52] microalbuminuria,[117,118] and cardiovascular events[48] are elevated before the clinical recognition of diabetes. Similarly, economic studies indicate that cost is elevated before the onset of clinical disease.[119,120] The few studies completed in individuals with unrecognized diabetes indicate elevated levels of chronic complications of diabetes, including elevated levels of nephropathy and peripheral neuropathy[121] as well as elevated estimated cardiovascular risk relative to those without diabetes.[122] Finally, in 2007 in the United States, the economic cost of undiagnosed diabetes was estimated to be $18 billion dollars, or $2864 per person with undiagnosed diabetes.[123,124] This estimate includes $11 billion in medical costs and $7 billion in indirect costs.[123,124]

Type 2 diabetes is an incurable relentless, progressive disease with significant associated complications and increased mortality risk, and recent studies demonstrate that even tight control of hyperglycemia in individuals with type 2 diabetes does not reduce associated complications and mortality.[125–127] The Veterans Affairs Diabetes Trial (VADT) is one of a series of recent clinical trials demonstrating that tight control of hyperglycemia does not reduce the risk of cardiovascular events or microvascular complications in individuals with poorly controlled longstanding diabetes.[125] In contrast, earlier studies of individuals with newly diagnosed diabetes had the opposite outcome. Results from the Diabetes Control and Complications Trial indicate that retinopathy and long-term incidence of CVD are lowered by tight control of hyperglycemia in individuals with early-stage type 1 diabetes.[128,129] Moreover, in the United Kingdom Prospective Diabetes Study (UKPDS), which enrolled individuals with newly diagnosed type 2 diabetes, HbA1c levels were a strong predictor of both microvascular and macrovascular complications.[130] Moreover, the early termination of the Look AHEAD (Action for Health in Diabetes) trial because of null results provides further evidence that prevention of diabetes comorbidities must occur before diabetes onset.[131] Look AHEAD tested whether a lifestyle intervention resulting in weight loss would reduce cardiovascular events in overweight and obese people with type 2 diabetes.

Based on the negative results of these recent trials that demonstrate the difficulty in preventing comorbidities once diabetes is clinically manifest, focus is shifting to identifying individuals at high risk for the disease as evidenced by clinical guidelines that present specific cutoffs for HgbA1c (5.7 to 6.4%) to diagnose pre-diabetes (ADA 2008[132]) and development of treatment guidelines by endocrine societies (ACE/AACE 2008[133]). The term *prediabetes* refers to individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) who do not yet meet the criteria for diabetes (see also **Chapter 4**). With use of HbA1c levels of 6.0 to less than 6.5% in NHANES 2003 to 2006, the prevalence of prediabetes in adults 20 years of age and older was estimated to be 3.1% in whites, 6.7% in African Americans, and 2.8% in Mexican Americans.[113] The prevalence of prediabetes is similar in men and women, 3.5% and 3.4%, respectively.[113] When the population was limited to adults 65 years of age and older, the prevalence of prediabetes increased substantially to 7.7% in whites, 13.2% in African Americans, and 8.3% in Mexican Americans.[113] Hence, the prevalence of prediabetes reflects the prevalence of diabetes in the population.

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31 The Quality Chasm

Diabetes Mellitus

Jason S. Fish

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Over the past several decades there has been much interest in refining the definition of quality of health care, moving the definition beyond an individual's perception of quality. A pivotal article by Avedis Donabedian in 1988 introduced the concept that quality of care can and should be measurable and that there will be multiple dimensions to identifying high-quality care depending on the perspective from which one is looking.[1] A provider may view quality in one way, a patient in another, and a payer in yet another. Furthermore, Donabedian introduced the idea that quality may be related not only to individuals delivering care but also to the systems in which care is delivered. Quality is likely influenced by structural attributes of the system or the processes of care used within the systems to deliver care.[1] Thus, quality becomes much broader than a health care provider's performance; it involves defining and measuring the structures and processes used by these providers and the systems delivering care. Shortly after this pivotal article, the U.S. Institute of Medicine (IOM) put forth a definition of quality of health care that encompassed Donabedian's conceptual model by stating that quality can be defined by how well health care itself aims at increasing the health outcomes for individuals and populations based on some set of agreed-on standards of care.[2]

With this broader definition of quality, the IOM examined the quality of health care in the United States; the culmination of this examination was the publication of two pivotal reports in 2000 and 2001 entitled "To Err Is Human: Building a Safer Health System"[3] and "Crossing the Quality Chasm: A New Health System for the 21st Century."[2] Coupled together, these reports raised significant concerns regarding the state of quality of care delivered by the U.S. health care system. In the second publication, the IOM cited an overwhelming amount of research illustrating the serious variation in quality of care across the nation across multiple settings (hospital, emergency, and ambulatory) and types of care delivered (acute, chronic, and emergent).[2] More specifically, the Quality Chasm report outlined how the U.S. health care system struggled with an overwhelming amount of overuse and underuse of services and errors in health care practice.[2]

After publication of these IOM reports, McGlynn and colleagues published results from an observational study corroborating the IOM observations, which identified that across 12 metropolitan areas involving 490 quality metrics for 30 acute and chronic conditions and preventative services, adults receiving care in the United States were only 54.9% likely to receive all of the evidence-based, recommended care.[4] Further analysis revealed that the variation occurred across all studied settings (hospital, emergency room, and outpatient) and types of care (acute, chronic, and preventative), with no single disease or specific clinical setting driving the low proportional use of guideline-recommended care.[4]

The Quality Chasm report[2] concluded, using Donabedian's quality framework of structure and process as related to outcome, that the United States health care system's struggle with achieving its expected or desired health outcomes is due to four key issues: increasing complexity of science and technology; increased prevalence of chronic conditions; poorly organized delivery systems; and constraints on exploiting the revolution in information technology.[2] In addition, the IOM put forth six specific aims for improvement to obtain comprehensive, consistent health care delivery.[2] The first aim is to optimize safety, focusing on avoiding injury or harm to patients in the context of health care delivery, including diagnostic evaluations, treatments, and the settings in which these are delivered. The second aim is to improve effectiveness, providing health care interventions based on evidence-based knowledge when possible. The third aim is to evolve toward more patient-centered health care delivery, offering care that is respectful of and responsive to individual patient preferences, needs, and values throughout the breadth of clinical decisions. The fourth aim is to improve timeliness of medical evaluation and treatment, reducing delays that are potentially harmful. The fifth aim is to improve efficiency, focusing on eliminating unnecessary processes to reduce cost, time, or use of resources. The last aim is to increase the equitable delivery of health care, providing care across populations with minimization of disparities based on individual patient characteristics, such as race and ethnicity, sex and other personal characteristics.[2]

ASSESSING THE QUALITY OF CARE FOR DIABETES

After publication of the IOM reports on health care quality, significant efforts to systematically improve the quality of health care delivery in the United States were undertaken. Given the increase in diabetes prevalence and the staggering

associated health care costs (see also **Chapter 1**), the quality of diabetes care has been a key area of focus to reduce the morbidity and mortality resulting from diabetic macrovascular and microvascular disease complications. To best characterize the quality of care for patients with diabetes, evidence-based metrics of assessment are needed. These metrics should be accurate, reliable, and valid with regard to associations with important patient-experienced clinical outcomes to determine the present level of quality of health care delivery and to prospectively analyze progress.[5] Furthermore, with valid and widely accepted measurements, there can also be accountability regarding achievement of objectives by patient, provider, or health care system.[5]

For diabetes, there are several different measurements endorsed by various professional organizations and societies for determining the quality of health care delivery (**Fig. 31-1**).[6] These measurements include traditional process measurements (e.g., measuring hemoglobin A1c [HbA1c]) and control process measurements (e.g., controlling HbA1c), sometimes called *intermediate outcomes*. It is important to note that none of the measures have been validated as surrogates for clinical outcomes such as retinopathy, end-stage renal disease, or cardiovascular disease, although some have been shown to be associated with potentially lowering the risk of development of these clinical outcomes.[7–10]

QUALITY-OF-CARE MEASURES

During the last decade, there have been several quality improvement projects aimed at improving quality of diabetes care through focusing first on process measurements such as measurement of HbA1c, blood pressure, and low-density lipoprotein (LDL) cholesterol (LDL-C) or screening for retinopathy or neuropathy. Multiple small randomized clinical trials were able to demonstrate the improvement of these diabetes process measures[6]; unfortunately, with additional research, improving these process measures has not consistently translated into improvements in the control of HbA1c, blood pressure, and LDL-C nor in improvements in relevant, patient-experienced diabetes clinical outcomes. In addition, when efforts were successful in improving control measures, control generally faded over time, particularly when feedback ceased.[6]

Focusing on control process measures of quality care improves achievement of therapeutic targets; yet, there is an increasing recognition that many factors outside the traditional health care system influence a person's health and thus the clinical relevance of these measures.[5,6] Provider actions, patient behaviors, comorbid conditions, medication safety, and cost have all been implicated to influence these measures and the achievement of therapeutic targets.[6] What has also complicated interpretation of research analyzing such control markers is the need for targets to be individualized for patients, taking into account patient comorbidities, life expectancy, and risk of therapy side effects.[6] Yet, setting thresholds too aggressively to define high-quality care for control measures may cause harm for some patients, and setting thresholds too liberally may lead to limited accountability or identifiable opportunities for improvement.[6,11–13]

IMPORTANCE OF THE HEALTH CARE PROVIDER-PATIENT INTERFACE IN ACHIEVEMENT OF HIGH-QUALITY CARE

Another area of focus as outlined in the IOM Quality Chasm report[2] is that patient-centeredness is an important aspect of improving quality, taking into account patient preferences.[2] Patients may choose goals or may decline care, and there may be patient characteristics that require amendment of metric goals or foregoing of the metrics altogether.[6] Other approaches have used the comparative analyses of composite scores (diabetes overall control scores), weighted measures (control of HbA1c assigned more points than measurement of HbA1c), and risk-based measures (adjusting for comorbidities affecting diabetes outcomes). However, these approaches have not been proven to improve diabetes outcomes more than the standard approach, and the complexity involved in implementation and measurement, including patient preferences, limits their widespread use.

A promising evolution of diabetes quality measurements is toward clinical action measures for which the assessment of

Process Measures	Control Process Measure / Intermediate Outcomes	Outcomes
HbA1c, % tested in last 12 months	Good blood glucose control (HbA1c < 8%)	Stroke/CVA
BMI, % tested in last 12 months	Poor blood glucose control (HbA1c > 9)	Amputation
Blood pressure, % tested in last 12 months	BMI ≥ 30 kg/m^2 (obese)	Heart disease
Lipids, % tested in last 12 months	Blood pressure (below 140/80 mm Hg)	Renal disease
Eye exam, % examined in last 12-24 months	Lipids, percentage of those tested with total cholesterol <190 mg/dl	Severe vision loss/retinopathy
Foot exam, % examined in the last 12 months	Lipids, LDL cholesterol < 100 mg/dl	
Microalbuminuria, % tests in the last 12 months		

FIGURE 31-1 Diabetes quality measures. BMI = Body mass index; CVA = cerebrovascular accident; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein.

quality is based on meeting one of four goals: (1) threshold met; (2) appropriate clinical action taken (e.g., starting or increasing the dose of an appropriate medication); (3) longitudinal assessment with resolution without intervention; or (4) identification of an exception such as a contraindication to further therapy intensification (e.g., a very low diastolic blood pressure) or maximal therapy already in use despite risk factor level without achievement of therapeutic target.[6] With continued improvement of electronic health records (EHRs), clinical action measures may prove an important way in which to measure quality, capturing provider action, patient preferences or attributes, and long-term effect.

SURVEY OF CURRENT QUALITY OF DIABETES CARE IN THE UNITED STATES

The main process measures for quality of diabetes care are (at least) annual measurement of HbA1c, lipids, blood pressure, and body mass index (BMI), and preventative measures including annual flu vaccine, testing for nephropathy, eye examination, and foot examination. The proportion of diabetes patients undergoing annual testing of HbA1c has been relatively stable over the past decade with a slight trend upward, in the high 80% range for most payers (**Fig. 31-2**).[14]

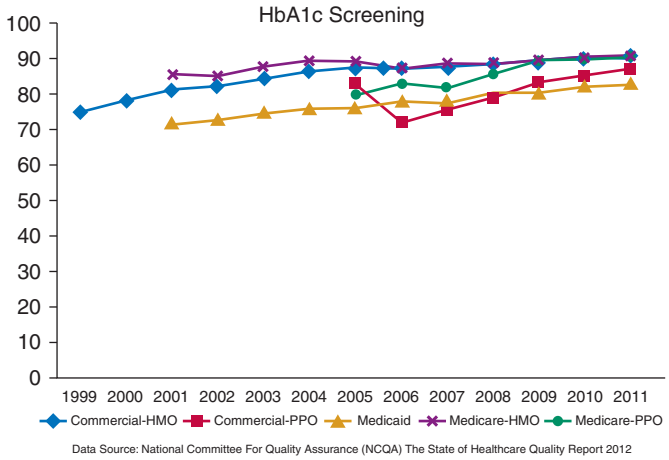


FIGURE 31-2 Rates of HbA1c testing among US adults with diabetes 1999-2011, stratified by type of health care coverage. *(Data from the National Committee For Quality Assurance (NCQA) The State of Healthcare Quality Report 2012. Available at: http://www.ncqa.org./Portals/0/SOHC-web1.pdf.)*

In 2010, the National Diabetes Surveillance System published self-reported data on several process measures (**Fig. 31-3**).[15] According to self-reports, 68.5% of patients had HbA1c measured at least twice per year, 62.8% received an annual eye examination, and 67.5% underwent an annual foot examination.[15] As discussed earlier, the past decade involved much effort toward improving process measures as evidenced by the relatively high percentage of patients undergoing HbA1c and LDL-C testing, blood pressure measurement, and nephropathy screening.

In examining control process measures of quality care, metrics associated more closely with outcomes, the United States national data for diabetes present some positive observations and some areas for improvement. The main control process measures are good glucose control (as reflected by HbA1c below 8%) as contrasted with poor glucose control (as defined as HbA1c above 9%); good blood pressure control (defined as blood pressure below 130/80 mm Hg); and good LDL-C control (defined as LDL-C below 100 mg/dL). In 2011, good HbA1c control (below 8%) averaged around 60% across multiple payers, ranging from 48% to 65% (**Fig. 31-4**).[14]

INCENTIVIZATION OR PAY FOR PERFORMANCE

Several major pay-for-performance (P4P) initiatives have reported their results for patients with diabetes. Unfortunately, the effect on quality from these initiatives remains controversial. Many studies indicate that improvements in measurements can be achieved; however, studies also indicate two important points: (1) once the financial incentive is removed, quality declines; and (2) once the quality targets are achieved, little improvement occurs afterward.[6] The largest P4P initiative, also cited as the most aggressive, is the U.K. Health System Quality and Outcomes Framework,

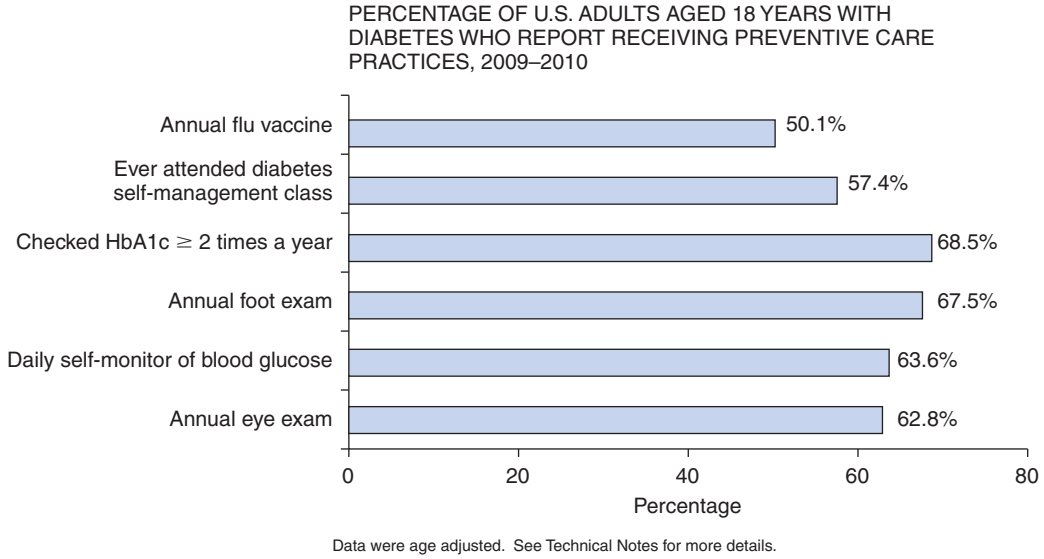


FIGURE 31-3 Self-reported preventative care for patients with diabetes, 2009 and 2010. *(Modified from National Diabetes Surveillance System, Behavioral Risk Factor Surveillance System data.)*

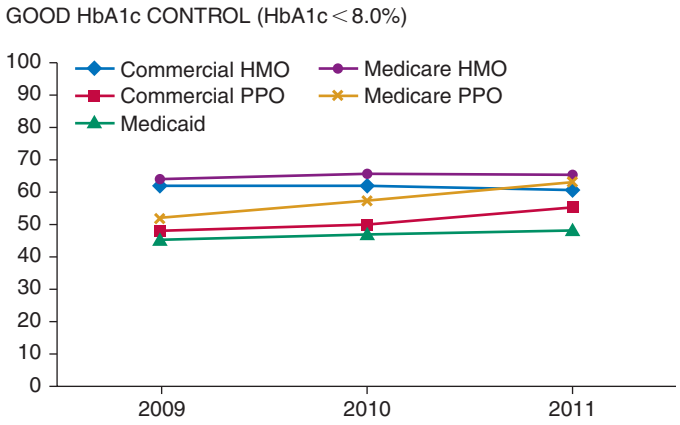


FIGURE 31-4 Proportion of United States patients with diabetes achieving good glucose control 2009-2011. HMO = Health maintenance organization; PPO = preferred provider organization. *(Modified from National Committee For Quality Assurance [NCQA]: The State of Healthcare Quality Report 2012.)*

introduced in 2004 as part of the General Medical Services contract. In this system, control of glucose improved dramatically with the program for many years. However, rates of quality for nonincentivized measures declined, and there was little improvement beyond the targeted glycemic goals.[6] In the United States, Kaiser Permanente is another system that has initiated diabetes performance measures aligned with financial incentives. Diabetes eye examinations and retinopathy screening were the focus of these measures. After initiation of the surveillance program, screening rates increased from 85% to 88%.[6] However, when the financial incentive was removed, the rates fell to below 80% (worse than baseline). More concerning are the findings of a cluster-randomized trial done using EHR-based diabetes clinical decision support to improve glucose and blood pressure control through the use of real-time feedback and incentives. In the trial, once the incentives and feedback ceased, even though the clinical decision support remained, the results of the quality measures decreased.[6] Despite these unintended consequences and difficulty with sustainability, these types of incentives continue to develop, including value-based reimbursements. Time will tell how effective they are or how they will need to be used to maintain the success and improvements sought.

EFFORTS TO IMPROVE CONTROL MEASURES

There have been many other initiatives focused on improvement of control measures for patients with diabetes; unfortunately, many of these efforts have failed. First, efforts to improve patient adherence have been evaluated in several studies.[16–19] Although there were many different methods used, such as diabetes education, home aides, or nurse-led training, only a small effect was seen in improving some control measures.[16,17] These efforts tended to be more associated with improvement in processes of care,[18] consistent with prior observations that treatment intensification has a greater influence on achievement of control measures than does targeting improved patient adherence.[19] Specifically, efforts aimed at improving treatment intensification have shown some short-term improvements in control measures and may be a source of future focus.[10,20,21] One area that has consistently produced improved achievement of control measures is group-based training for self-management strategies. Several studies have demonstrated improved HbA1c, diabetes knowledge, systolic blood pressure, and BMI and a reduction in the need for medications with such group-based intervention programs.[22]

Recently, a promising new model was introduced aiming to help identify more accurately the measurements needed to improve outcomes with accountability tied to the measures (**Fig. 31-5**).[5,23] The model emphasizes areas of control and the primary drivers that affect health outcomes. In this model, health care (high control) accounts for 20% of control of improving health; health behaviors (shared between health care and patient) account for 30%; and socioeconomic and

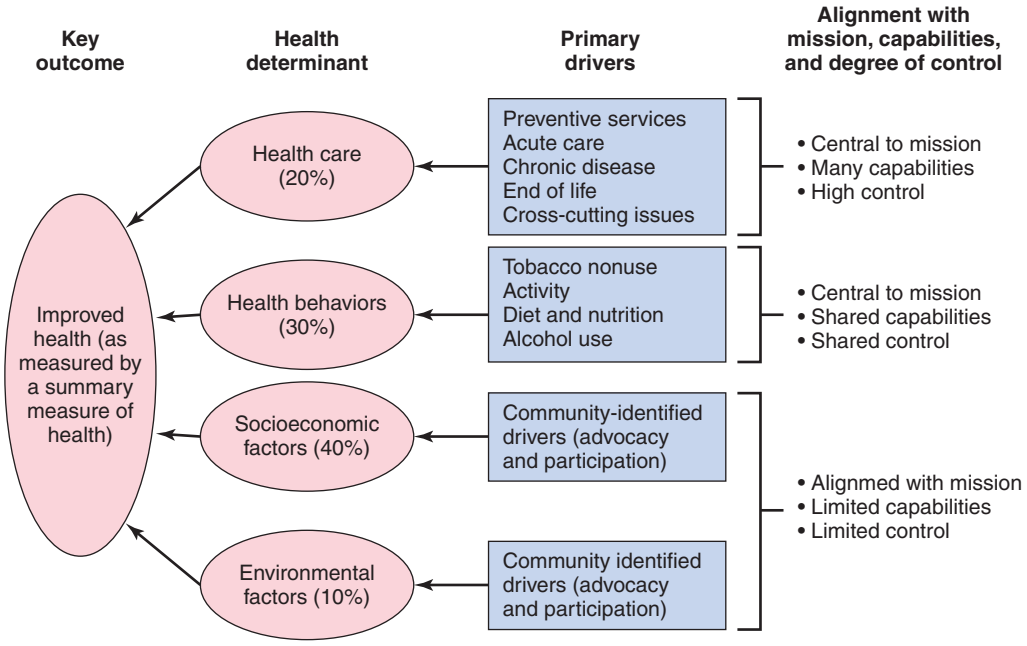


FIGURE 31-5 Framework of the drivers of health determinants.

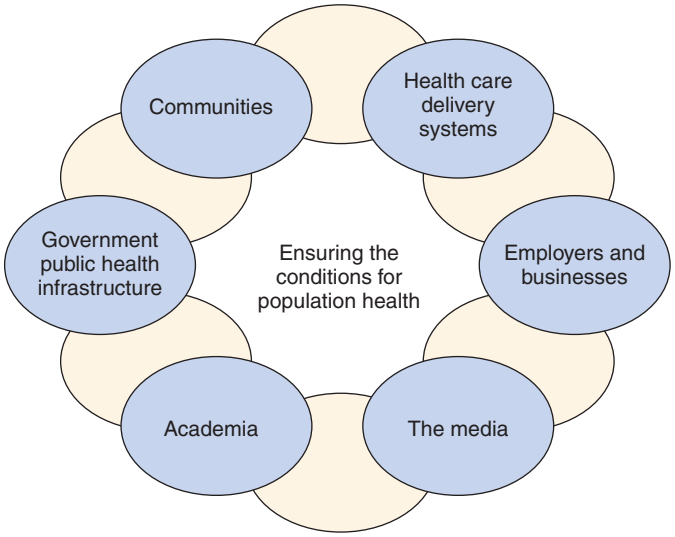


FIGURE 31-6 The intersectoral public health system. Ensuring population health.

environmental factors accounting for the remaining 50%. With this model, more relevant quality measurements with realistic accountability can be developed.

SUMMARY

In summary, the IOM reports identifying the quality chasm a decade ago remain relevant for contemporary patients with diabetes. Overall, the quality of health care remains inconsistent, with continued variation across the nation, fragmented care lacking coordination, and a remarkable level of investment with little improvement in overall health outcomes.[5] Physicians practicing within engaged health systems, focused on improving processes, are continuing to struggle to translate these process improvements into better patient outcomes.

As illustrated in **Figure 31-6**, health is not defined simply by what happens when patients engage the health care system. There are many key stakeholders that need to be engaged, with health care systems playing a vital part.[24,25] If the health care system is to improve the health of patients with diabetes, given the overwhelming rates of diabetes and all of the sequelae associated with diabetes including health-related costs, then new models of care are going to be needed to improve these outcomes, holding accountable those responsible for each part as well as continuing to improve on diabetes quality measurements.

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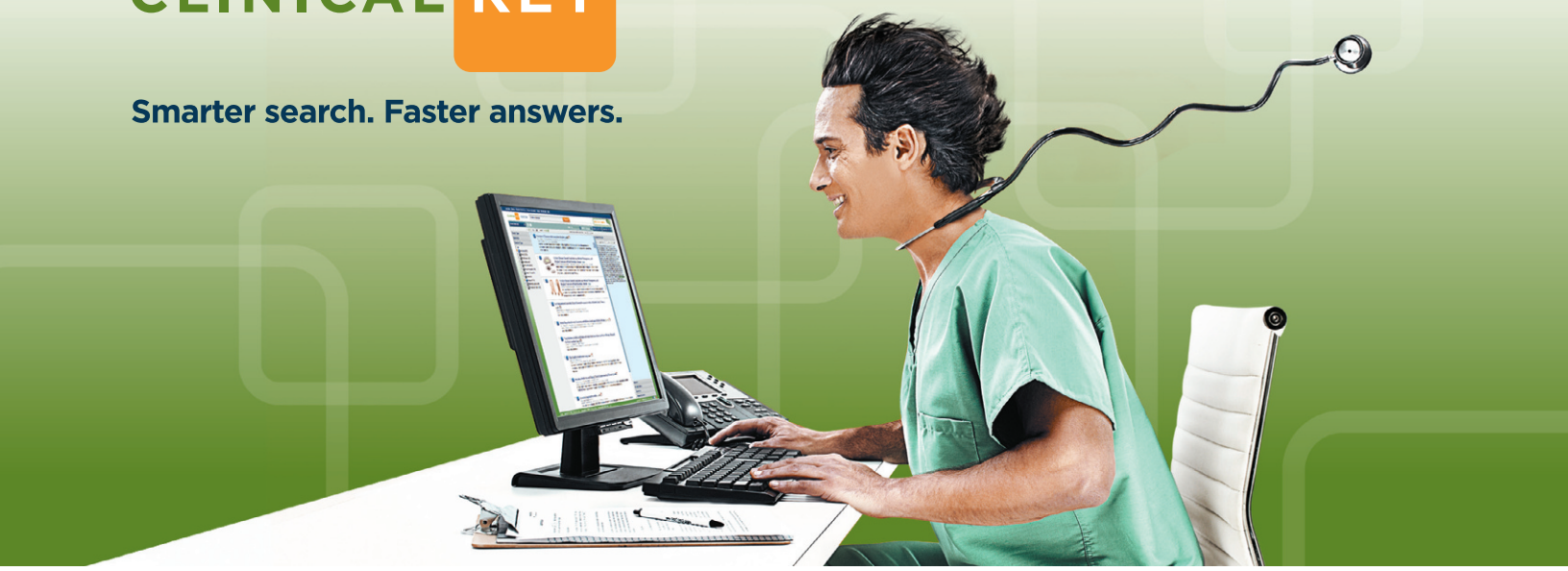
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